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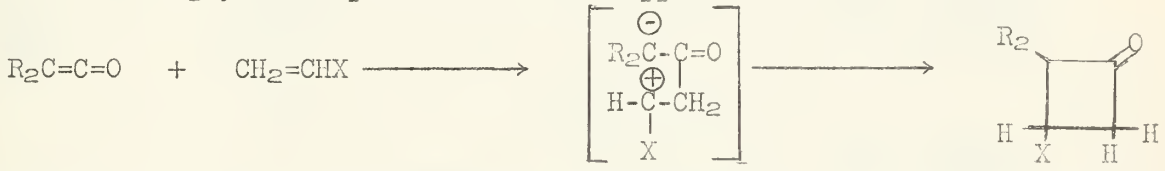
CYCLOADDITION REACTIONS OF KETENES

Reported by R. J. Johle February 8, 1965

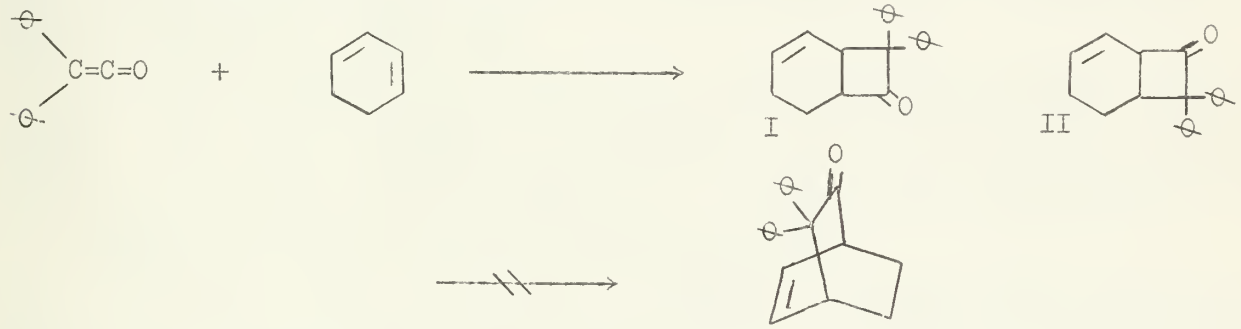
Introduction: It is well known that ketenes add to a number of olefinic compounds to form cyclobutanone derivatives.[4a] In most reactions ketene itself adds much less readily than disubstituted ketenes to double bonds, and only a few such reactions have been known until recently. Diphenylketene and dimethylketene have been studied more than any other members of the series.

The preparation and non-cyclic addition reactions of ketenes are well reviewed in several places[1] and will not extensively be dealt with here. The purpose of this seminar is to present a summary of the reactions of ketene and disubstituted ketenes which lead to cyclobutanone formation. The special cases of β-lactam formation from the cycloaddition of ketenes to carbon-nitrogen double bonds[2], and the formation of β-lactones by the cycloaddition of ketenes to carbonyl compounds[3] have been well reviewed. Of the work available in earlier reviews (general cyclobutanone formation,[4] cycloaddition to enamines,[5] and cycloaddition to acetylenic ethers[6]), only points considered essential to an appreciation of the present discussion are included.

The mechanism of cyclobutanone formation from ketenes and olefins has not been ascertained; structures are compatible with a diradical mechanism or with an ionic process involving nucleophilic attack by the olefin.[4a] The ease of cycloaddition of ketenes to the strongly nucleophilic enamines supports the ionic mechanism.[7]



Early Work on the Cycloaddition of Ketenes to Olefins: The first observation of a cycloaddition reaction between a ketene and an olefin was made by Staudinger and Suter when they showed that diphenylketene added to the double bonds of cyclopentadiene, styrene, and cyclohexene to give cyclobutanones.[8] Farmer and Farooq showed that the reaction between diphenylketene and cyclohexadiene was not a simple Diels-Alder reaction (such as the 1,4-addition of acrolein to cyclohexadiene) since the adduct from cyclohexadiene consists always of a single mono-olefinic substance, and this passes on hydrogenation into a dihydride identical with the adduct formed directly from the reagent and cyclohexene.[9]



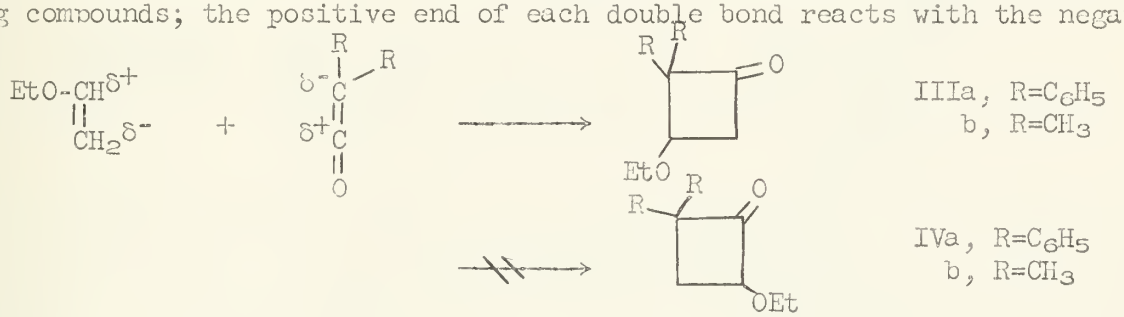
The problem of deciding whether the product was (I) or (II) was shown definitely by the nature of the degradation products obtainable from the adduct. Supporting evidence for the formation of (I) can be obtained from the earlier work by Staudinger[10] where he showed that substances of the type HX (hydrogen halide, hydrogen sulphide, amines, organic acids, etc.) form addition products with members of the ketene group uniformly according to the equation $CRR'=C=O + HX \rightarrow CHRR'\underset{X}{C}=O$.

It appears that in all the numerous observed examples in which a dividing addendum adds to the ethylenic center of a ketene, polarization of the latter occurs exclusively in the direction $\overleftarrow{CRR'}=C=O$. For the second group of reactions, those in which members of the ketene group function as undividing addenda, instead of compounds in which addition is made, the polarizing tendency also seems to be present. Thus it was found that a conjugated diene will always combine with the ketene in manner (A) rather than give the isomeric form (B).

(A) (B)

Staudinger and Meyer were unable to obtain a cycloadduct between dimethylketene and styrene,[11] and it was concluded that diphenylketene was much more reactive than dimethylketene. Hasek and coworkers have shown that dimethylketene does react with p-methoxystyrene and thus the electron-donating effect of the alkoxy group tends to make the olefinic bond more nucleophilic and the reaction proceeds.[12]

Cycloaddition of Ketenes to Vinyl Ethers: The cycloaddition of diphenylketene to vinyl ethers was first noted by Staudinger and Suter in 1920.[8] A few years ago, Hurd and Kimbrough reexamined the cycloadduct of diphenylketene and ethyl vinyl ether,[13] and corrected Staudinger's original structural assignment by demonstrating that the product was 3-ethoxy-2,2-diphenylcyclobutanone (IIIa) and not 4-ethoxy-2,2-diphenylcyclobutanone (IVa). The authors suggested that diphenylketene and ethyl vinyl ether should react to give (IIIa) considering the bond polarizations of the two starting compounds; the positive end of each double bond reacts with the negative end of



IIIa, R=C_6H_5
b, R=CH_3

IVa, R=C_6H_5
b, R=CH_3

the other. No evidence was cited as to why the ethyl vinyl ether should be polarized in the way they claimed; however, the electron donating effect of the ethoxy group would tend to place greater electron density on the $-CH_2$ group. The argument still seems to be unreasonable on thermodynamic grounds since the reactions are not exothermic enough to have transition states closely resembling starting materials. Hasek and coworkers do agree that polarity is an important factor in the reactivity of nucleophilic olefins with ketenes, but they observed that the symmetrical vinyl ether, 1,2-diethoxyethylene, added to dimethylketene to give 3,4-diethoxy-2,2-dimethylcyclobutanone in 20% yield.

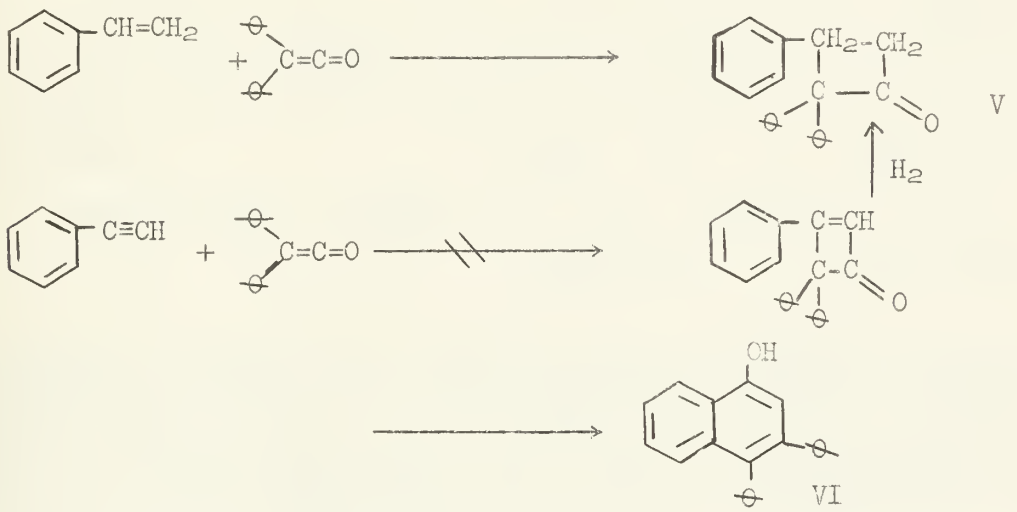
Staudinger reported the cycloaddition of dimethylketene to ethyl vinyl ether;[11] however, he did not report the yield or structure for the cycloadduct. Hasek and coworkers were able to prepare the cycloadduct in 80% yield by adding dimethylketene to ethyl vinyl ether at room temperature.[12] Thus it was shown that with the more nucleophilic character of the olefinic bonds of vinyl ethers, dimethylketene and diphenylketene reacted at approximately the same rate.

Kimbrough was unable to prepare cycloadducts of diphenylketene and alkyl vinyl ethers higher than ethyl vinyl ether.[14] Hasek and coworkers have reported that dimethylketene reacts readily with higher alkyl ethers to form alkoxycyclobutanones in good yields.[12] Inert substituents, such as chloro and phenoxy on the alkyl group, had no adverse effect on the reaction. Ethyl propenyl ether formed an adduct with dimethylketene in good yield although ethyl isobutenyl ether failed to react. The latter addition presumably failed because steric effects override the nucleophilic reactivity of the vinyl ethers. As will be seen latter in the seminar, the more nucleophilic enamines of analogous structures (isobutenyl amines) react readily with ketenes.[7] Steric effects were also noted in the cycloaddition of dimethylketene to cyclic structures. Dihydropyran was very reactive with dimethylketene, but n-butyl 1-cyclohexene-1-yl ether failed to react.

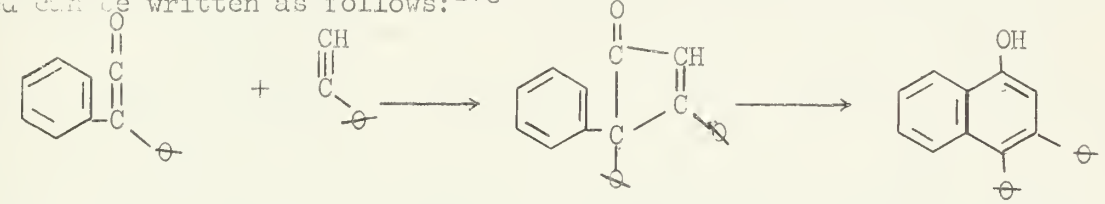
Cycloaddition of Ketenes to Allyl Ethers: Hasek and coworkers have observed that the nucleophilic character of the olefinic linkage is sharply reduced in allyl ethers.[12] They were unable to prepare cycloadducts of dimethylketene and allyl ethers since the rapid dimerization of dimethylketene prevented the use of high temperature. However, the rates of dimerization of dialkylketenes fall off rapidly with increase in

size and branching of alkyl groups. At room temperature approximate rate constants ($k \times 10^6$) are as follows: dimethyl-, 70; ethylmethyl-, 10; diethyl-, 0.2; butylethyl-, 0.04; and ethylisobutyl-, 0.006. Thus higher dialkylketenes could be forced into cycloaddition with allyl ethers at elevated temperatures.

Cycloaddition of Ketenes to Acetylenic Compounds: The addition of ketenes to acetylenic compounds has met with many interesting problems. In 1937 Agre sought to obtain further evidence that styrene and diphenylketene reacted to form a cyclobutanone derivative.[15] His plan of attack involved addition of diphenylketene to phenylacetylene; assuming that styrene and phenylacetylene would add to the ketene in the same way, then reduction of the product from the acetylenic hydrocarbon should give the adduct (V) of the ethylenic hydrocarbon. Agre did obtain a product from the reaction



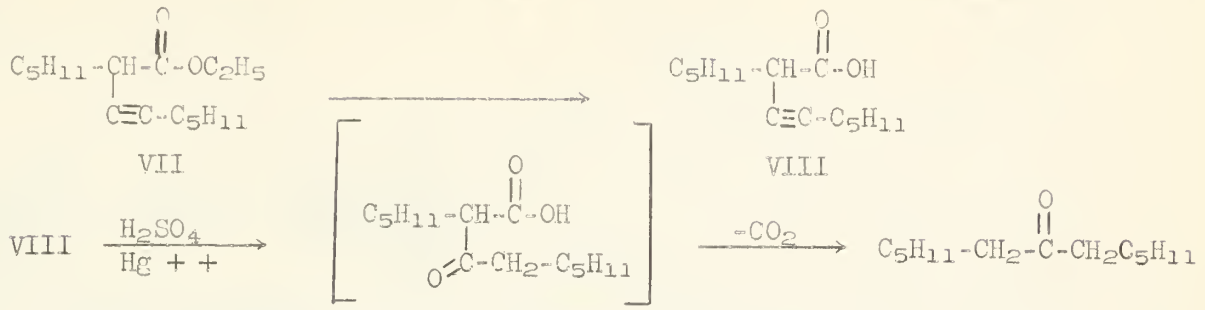
of the two materials, but did no further work on it. Smith and Hoehn showed that the product was not a cyclobutanone, but was actually 3,4-diphenyl-α-naphthol (VI).[16] In subsequent experiments the authors were able to propose a mechanism for the formation of the α-naphthol. They observed that the aryl group in the 3-position of the resulting 3,4-diaryl-α-naphthol is supplied by the acetylene;[17a] that the ketone $C_6H_5CH_2C(=O)C\equiv C-C_6H_5$ is not an intermediate in the formation of the naphthol since it cannot be cyclized to the product;[17b] and that the β-naphthol is not formed.[17c] It was also shown that diphenylketene reacts with disubstituted acetylenes and thus a hydrogen atom attached to an acetylenic carbon atom is not required.[17d] The mechanism which the authors proposed can be written as follows:[17e]



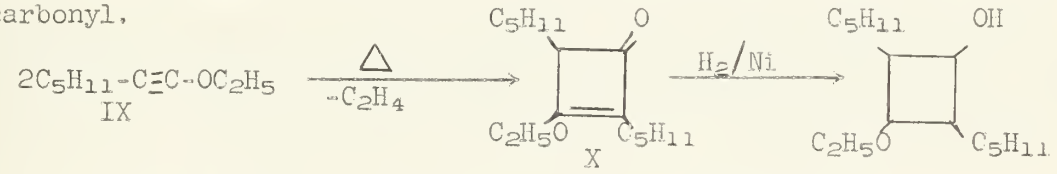
No conclusive evidence was presented for this mechanism since the intermediate cyclobutanone could not be isolated. The authors stated that the mechanism accounts for all the facts and serves as a useful working hypothesis.

No further papers on reactions of acetylenic compounds with ketenes were published until the cycloaddition of ketenes to alkoxyacetylenes was first suggested by Nieuwenhuis and Arens[18] whose interpretation of Ficini's earlier work[19] showed that pyrolysis of ethoxyacetylenes gave ethoxycyclobutenones. Ficini observed that 1-ethoxy-1-heptyne (IX) when heated at 120-130° evolved ethylene in a smooth reaction. From the slightly colored reaction mixture she isolated a substance, which according to its composition was formed from two molecules of the alkynyl ether minus one molecule of ethylene. She proposed structure (VII) for this compound, mainly on the grounds that on alkaline hydrolysis a monobasic acid (VIII) was formed; and on treatment with concentrated sulfuric acid and mercuric oxide, dihexyl ketone was obtained.

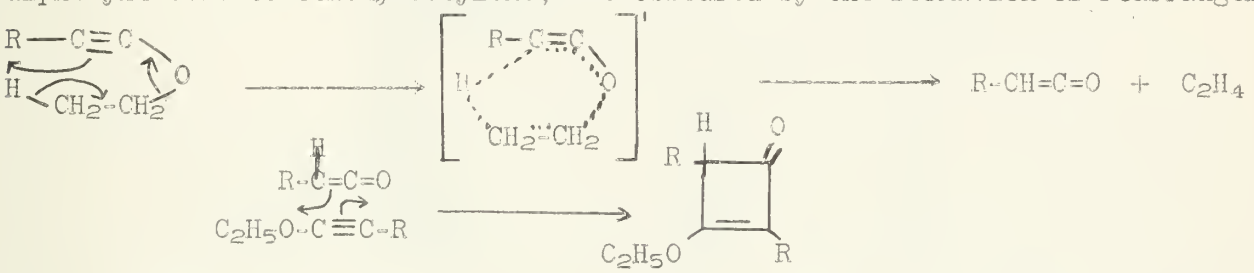
When Nieuwenhuis and Arens repeated the experiment they obtained the same product,



however, they determined the infrared spectrum which Ficini had not done.[18] They observed a carbonyl band, but no band arising from a doubly substituted triple bond. Instead, there was a strong band indicating the presence of a double bond. The authors thus proposed structure (X) which was shown to be the correct one since upon hydrogenation, two moles of hydrogen were absorbed and the infrared spectrum of the tetrahydroderivative showed the presence of a hydroxyl group and the absence of an ester carbonyl.

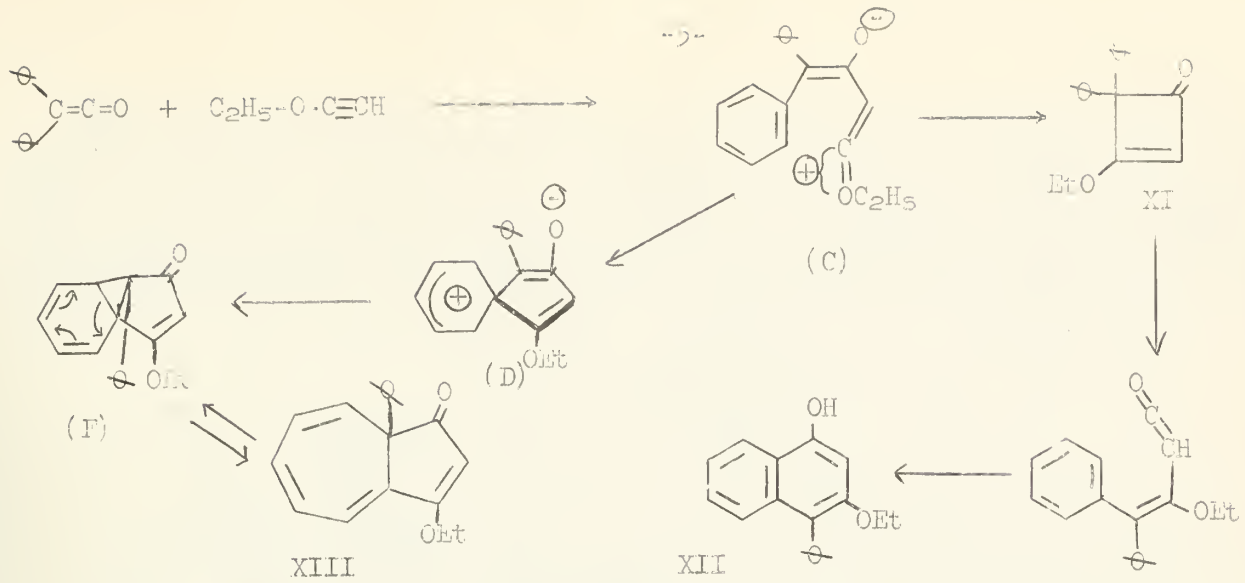


The reaction was shown to be applicable to other alkynyl ethers and also to ethoxy-ethynyl carbinols. The reaction apparently involves a concerted elimination of a ketene substituted ketene from the ethoxyacetylene, followed by cycloaddition of the ketene and acetylenic ether. Ketene formation can easily be explained with the assumption of a cyclic transition state. Proof of this mechanism, by addition of diphenylketene to ethoxyacetylene, was obscured by the formation of rearrangement

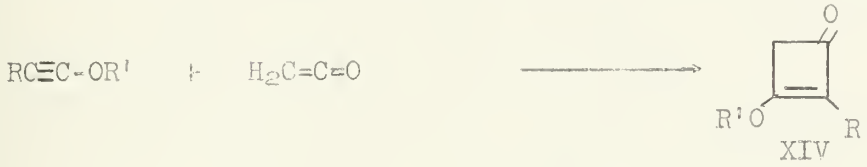


products[6,20] and by a peculiar mode of addition involving a benzene nucleus of the diphenylketene.[21,22] Nieuwenhuis and Arens observed that the cycloaddition of diphenylketene to ethoxyethyne was very dependent upon the solvent employed.[20] In benzene at room temperature, a 34% yield of 1-phenyl-2-ethoxy-4-hydroxynaphthalene (XII) was obtained, whereas in nitromethane at -20° the product was assigned the structure of 1,1-diphenyl-2-ethoxycyclobut-2-ene-4-one (XI). They subsequently withdrew the proposal of (XI), but without an alternative formulation.[6] Barton and coworkers,[21] and Woodward and coworkers[22] independently solved the problem.

The latter group has postulated that in the first step of the reaction the ethoxyacetylene probably adds to the carbonyl group of the diphenylketene. The zwitterion (C), in part, yields the cyclobutenone XI. (C) can also convert by way of the spirocarbonium ion (D) into the norcaradiene derivative (E) and thence to 1-ethoxy-3-oxo-3a-phenyl-3, 3a-dihydroazulene (XIII). Upon gentle heating, XI is converted into XII.

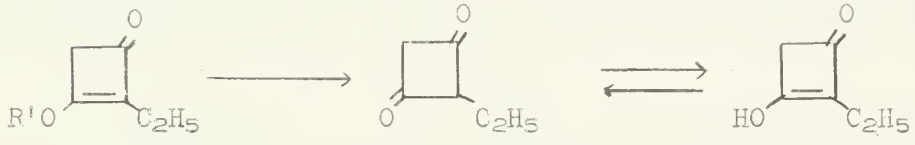


Rosebeek and Arens were able to prepare cyclobutenone ethers of type (XIV) by reacting ketene with 1-alkoxy-1-alkynes at 0° in nitromethane.[23] They observed that the ethers (XIV), R=C_2H_5, R'=CH_3 or C_2H_5 on exposure to laboratory air, hydrolyze with formation of 1-ethoxy-cyclobutane-2,4-dione. Wasserman and Dehmlow concur-



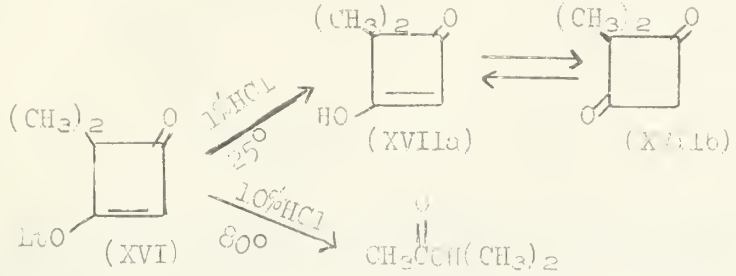
Alkoxyalkyne RC≡COR'		Yield in %
R	R'	
CH_3	t-C_4H_9	51
C_2H_5	CH_3	30
C_2H_5	C_2H_5	35
C_2H_5	t-C_4H_9	52
t-C_4H_9	C_2H_5	34
n-C_5H_{11}	C_2H_5	56

rently prepared compounds of type (XIV) by forming ketene *in situ* by the addition



of an acid chloride and a tertiary amine; the ketene then reacted with the alkoxyacetylene to form the cyclobutenones.[24] The formation of alkoxycyclobutenones was traced in the reaction mixture by the observation of the characteristic strong infrared bands near 1755 and 1580 cm^{-1}, and a peak of medium intensity at about 870 cm^{-1}. Thus they were able to detect substantial amounts of the cyclobutenone formed when ketene was bubbled through a solution of ethoxyacetylene in methylene chloride. The separation of the cycloadduct from ethoxyacetylene, acetone, diketene, and polymeric products was accomplished by repeated column chromatography and crystallization from ether-pentane at -50°. The cycloadduct (XV) is stable at low temperatures, but polymerized exothermically when heated to 65°. When XV is stirred with moist ether, ring opening takes place with formation of β-ethoxycrotonic acid, while with hot anhydrous ethanol the corresponding ethyl ester is produced.

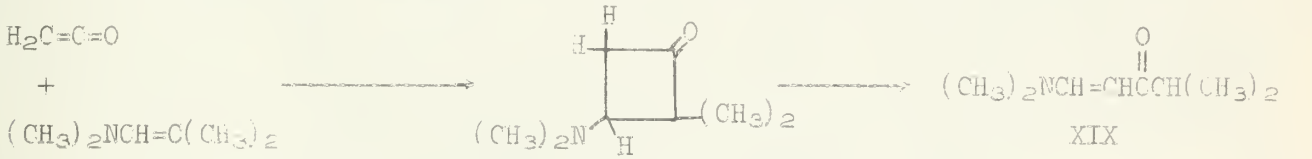
Hasek and coworkers have reported the cycloaddition of dimethylketene to ethoxyacetylene to form 3-ethoxy-4,4-dimethyl-2-cyclobuten-1-one, (XVI). Unlike the ketene and diphenylketene adducts of ethoxyacetylene, the dimethylketene cycloaddition product is stable at temperatures up to 150°, at which point a mildly exothermic reaction starts. The high-boiling products of this reaction have not been identified. The hydrolysis of (XVI) in 1% hydrochloric acid solution gave 2-hydroxy-4,4 dimethyl-2-cyclobuten-1-one (XVIIa). More vigorous hydrolysis in hot 10% hydrochloric acid



solution gave only 3-methyl-2-butanone. The hydrolysis product of (XVI) in the solid state or dissolved in polar solvents (DMF, DMSO, pyridine, acetone) exists as the enol (XVIIa); in chloroform it exists as 2,2-dimethyl-1,3-cyclobutanedione (XVIIb). The authors showed that (XVI) may be regarded as the ethyl ester of the strongly acidic enol (XVIIa) since it undergoes ammonolysis and aminolysis reactions in which the ethoxy group is replaced by an amine moiety.

Hasek and coworkers have also shown that cycloaddition takes place on the acetylenic rather than the olefinic bond when dimethylketene was added to the acetylenic vinyl ether, 1-buten-3-ynyl methyl ether to give (XVIII).

Cycloaddition of Ketenes to Enamines The cycloaddition of ketenes to enamines to produce cyclobutanone derivatives was reported nearly simultaneously by several groups. In a series of communications, Opitz and coworkers observed that cyclobutanone derivatives were formed by dropping an ether solution of an acid chloride into a mixture of an enamine and triethylamine.[26] Hasek and Martin[27] prepared a cyclobutanone by reacting N,N-dimethyl-isobutenylamine and dimethylketene. However when they used ketene, they observed that upon heating the cyclobutanone it rearranged to 1-dimethylamino-4-methyl-1-pentene-3-one (XIX). Berchtold, Harvey, and

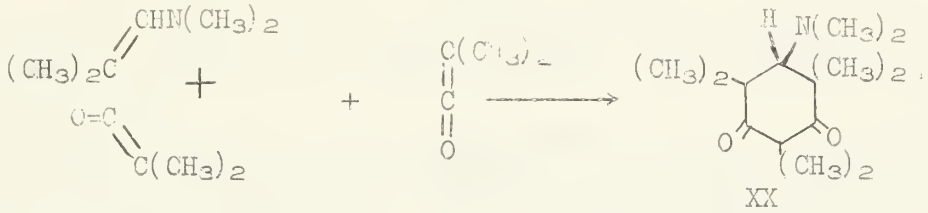


Wilson also noted the same type of thermal rearrangement with the cyclobutanone from 1-N-morpholinoisobutene and ketene.[28]

All three groups have been able to show that addition products with enolizable hydrogens are thermally unstable and rearrange to aminovinyl ketones upon heating. Hasek and coworkers have prepared cycloaddition adducts from several dialkylketenes and a variety of enamines derived from secondary aldehydes and secondary amines.[7] In general, the reaction was more sluggish with enamines from higher aldehydes, and higher dialkylketenes also exhibited less reactivity. The effect of substituents on the nitrogen atom of the enamine was less obvious.

The order of addition of the reactant was important to obtain optimum yields with enamines, as was the case with vinyl ethers. Best results were obtained by addition of the dialkylketene to a solution of the enamine. In the cycloaddition of dimethylketene and N,N-dimethylisobutenylamine, either simultaneous or reverse addition lead to large amount of dimethylketene polymers.

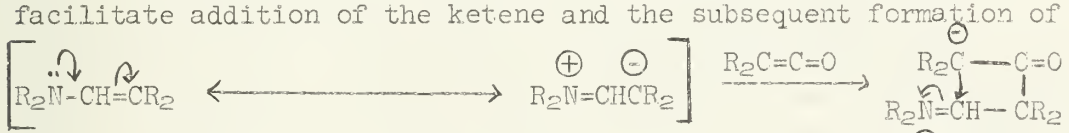
When highly polar solvents were used, the rate of the cycloaddition reaction was increased, as evidenced by a more exothermic reaction. In addition to the 1:1 adduct, appreciable quantities of 2:1 and 3:1 dialkylketene-enamine adducts were formed. Cycloaddition of equimolar quantities of dimethylketene and N,N-dimethylisobutenylamine in acetonitrile gave 24% of the 1:1 cycloadduct, 32% of a 2:1 adduct (XX), and 9% of a 3:1 adduct which has not been elucidated.



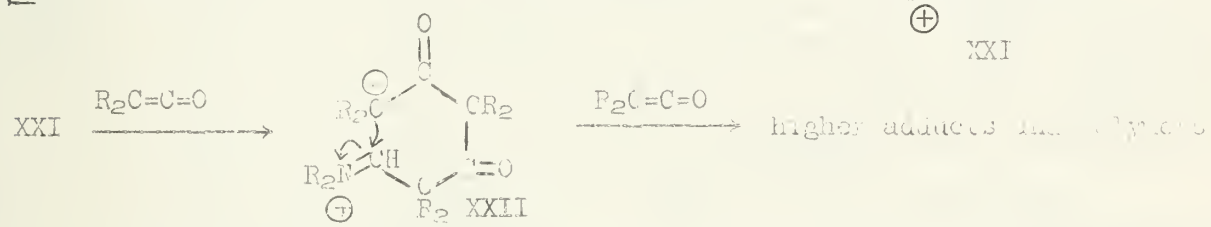
XX

Hasek and coworkers have found that vinyl ethers, unlike enamines, do not form 1:2 and 1:3 adducts with dimethylketene and have tentatively suggested that the cycloaddition of ketenes to vinyl ethers is a more concerted process than the addition to enamines.[12]

The ease of cycloaddition of ketenes to the strongly nucleophilic enamines supports the ionic mechanism of cyclobutanone formation.[7] This is bolstered by the effect of polarity of the solvent on the rate of reaction, and by the formation of by-products ranging from 2:1 adducts to ketene polymers. Stabilization of the charge separation in the ionic intermediates XXI and XXII, might be expected to facilitate addition of the ketene and the subsequent formation of the higher adducts.



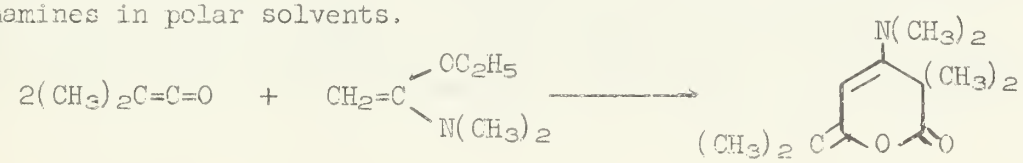
XXI



XXII

In view of the facile addition of ketenes to enamines and vinyl ethers, Hasek and coworkers extended their work to the investigation of the reactions of ketenes with ketene-O,N-acetals and ketene-N,N-acetals.[29] Ketene-N,N-acetals with hydrogen atoms on the olefinic carbon atom were found to react vigorously with dimethylketene to form acylketene-N,N-acetals, this can be compared with that of the enamines containing β-hydrogen atoms. However, no spectral evidence of intermediate cyclobutanone formation could be found when the reaction was carried out below 0°. The authors were unsuccessful in preparing a dimethylketene-N,N-acetal without olefinic hydrogen atoms. They did observe that dimethylketene did not react with the dimethylketene-O,N-acetal, 1-ethoxy-N,N-dimethylisobutenylamine. The olefin, in this case, behaved like an isobutenyl ether rather than an isobutenyl amine.

The authors also observed that 2 moles of dimethylketene reacted with 1 mole of the ketene-O,N-acetal, 1-ethoxy-N,N-dimethyl-vinylamine, in acetonitrile to give the pyranone (XXIV). This is analogous to the formation of 2:1 adducts of ketenes with enamines in polar solvents.



XXIV

Conclusion. The ease of cycloaddition of ketenes to highly nucleophilic compounds such as enamines, ketene acetals, and acetylenic ethers favor the ionic process of cycloaddition of ketenes to olefins to form cyclobutane derivatives. This is

further substantiated by the lack of cycloaddition to the less nucleophilic allyl ethers. The order of reactivity of ketene, dimethylketene, and diphenylketene in cycloaddition reactions appears to be regulated by polarity and steric effects.

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KETENIMINES

Reported by Joseph C. Catlin February 15, 1965

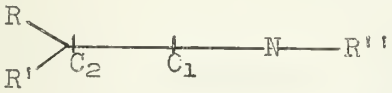
In this seminar we will consider the structure, preparation, and reactions of ketenimines(I). Ketenimines were previously reviewed in an Illinois seminar in [illegible].[1]

(I) $\rangle C{=}C{=}N-$

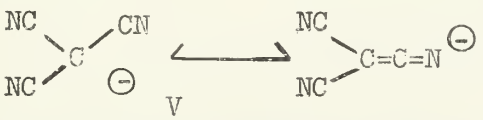
Wheatley studied the structure of N-methyl-2,2-bis(methylsulphonyl)-vinylidene-amine(II). He observed several unusual features. The molecule had a P_{bcn} space group, and the crystal contained four molecules per unit cell. This information is sufficient to show that the vinylideneamine (II) has either a center of symmetry or a two fold axis. This establishes that the vinylideneamine (II) is linear. Wheatley also completed a 3-dimensional analysis. He found that the C_1-C_2 bond is of double bond length; unexpectedly the C_1-N bond is of triple bond length (See Table 1).[2] Wheatley and Bullough determined the structure of N-methyl-2-methylsulphonyl-2-phenylsulphonylvinylideneamine (III). In this case, as in the previous case, the C_1-C_2 bond was found to be of double bond length, and the C_1-N bond was found to have the length of a carbon-nitrogen triple bond. In this case, the C_1-N-R angle is not 180° but 170.6°. The authors felt that this deviation of the vinylideneamine (III) from linearity is caused by the packing of the molecule within the crystal. The C_1-N-R angle is such that the N-methyl group (R) is an equal distance from its nearest neighbors, two oxygen atoms. Wheatley and Bullough suggested that the sulphonyl groups may tend to withdraw non-bonded electrons from nitrogen and give rise to a hyperconjugative effect between the nitrogen and the N-methyl which would be at a maximum when the C_1-N-R angle was 180°.[3] Reasoning that N-ethyl should hyperconjugate to a lesser extent than N-methyl, Daly studied N-ethyl-2,2-bis(methylsulphonyl)-vinylideneamine (IV) and found the C_1-N-R bond angle to now be 144.5°, the N-R bond to be longer, and the C_1-N bond to have less triple bond character.[4] Comparative molecular dimensions are given in Table 1.

TABLE 1

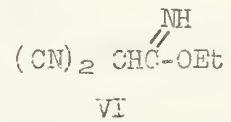
	$R{=}MeSO_2{-}{-}{=}R'$ $R''{=}Me$ (II)[2]	$R{=}MeSO_2{-}$ $R'{=}ArSO_2{-}$ $R''{=}Me$ (III)[3]	$R{=}MeSO_2{-}{-}{=}R'$ $R''{=}Ethyl$ (IV)[4]	For comparison[5]	
C_1-C_2	1.342	1.354	1.356	C=C	1.337±.006(av)
C_1-N	1.154	1.148	1.165	C=N	1.34±.05(CH_2N_2)
				C≡N	1.158±.002(av)
N-R	1.426	1.382	1.465	C-N	1.472±.005(av)
$\angle C_1NR$	180°	170.6°	$144^\circ31'$	$R_2C{=}N^{OH}$	113°



Cyanocarbon acids form a class of strong acids which are stabilized by resonance(V).[6]



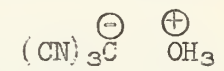
V



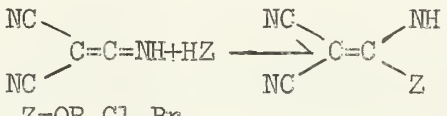
VI

The simplest cyanocarbon, cyanoform, was first made by Schmidtmann in 1896 by reaction of the sodiomalononitrile with cyanogen chloride. He isolated the sodium and the silver salts.[7] He also isolated products from the reaction of ethanol and methanol with cyanoform.[7] Hantzsch and Osswald proposed structure VI for the adduct formed from cyanoform and ethanol. They also observed that an amine salt formed when a solution of cyanoform is saturated with ammonia, and they emphasized the strong acid character of cyanoform.[8] We shall consider the correctness of structure VI in more detail later. Cox and Fontaine found that Schmidtmann's method gives small yields of a product of doubtful purity. Cox and Fontaine observed that the reaction of potassium cyanide with the bromide of malononitrile gave "very

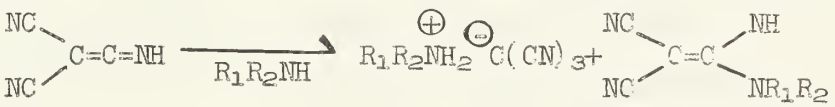
pure" cyanoform in greater than 80% yield. Their cyanoform, an uncolored crystal, fused at 55-56° and was very soluble in organic solvents. The potassium salt was insoluable in neutral organic solvents but soluable in water and absolute alcohol. The authors were unable to obtain reproducible nitrogen analysis on their cyanoform.[9] A pKa value of 2.04 was obtained by adding an equivalent amount of sulfuric acid to the barium salt of cyanoform and determining the pH of the resulting solution.[6] More recently a new pKa value was determined for cyanoform after the construction of an H_- acidity scale. The more recent pKa value obtained was approximately -5 (in $HClO_4$ -5.13, H_2SO_4 -5.00).[10] This can be compared with a pKa value for hydrochloric acid of -7.[11] Trofimenko and co-workers report that the reaction of potassium cyanide with the dibromide of malononitrile gives higher yields of a purer product,[12] than the method of Cox and Fontaine where the monobromide is used.[9] Trofimenko has isolated cyanoform as a crystalline solid having physical properties unlike those reported by Cox and Fontaine. He suggested VIIa as the structure of cyanoform in the free-state, and VIIb as the structure in aqueous etheral solution. As proof of structure VIIa he sites the absence of ketenimine absorption at 1920-2000 cm^{-1} and the presence of bands at 2500, 2280, and 1790 cm^{-1} which he suggests are similar to immonium bands.[13,14] This structure

VIIa  VIIb 

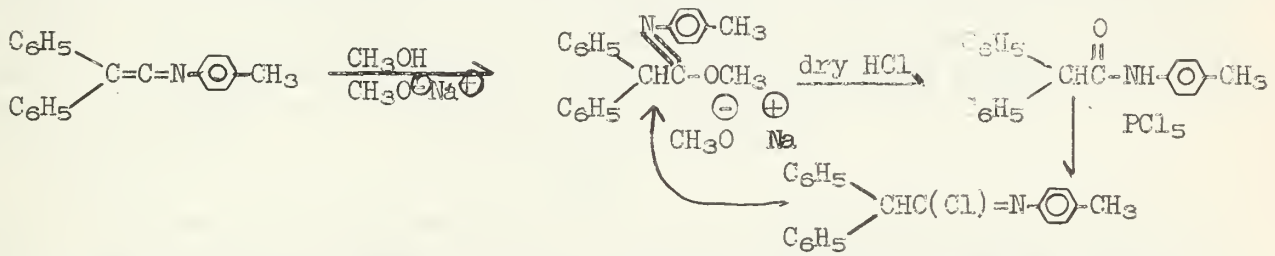
is analogous to the one previously suggested, after X-ray analysis, for ketenimines with electron withdrawing substituents on the carbon.[2,3,4]
Trofimenko and co-workers report that cyanoform reacts with hydrobromic acid and alcohols and confirm that it reacts with hydrochloric acid (VIII). Cyanoform reacts with amines to form both salts and addition products (IX).[12]

VIII 

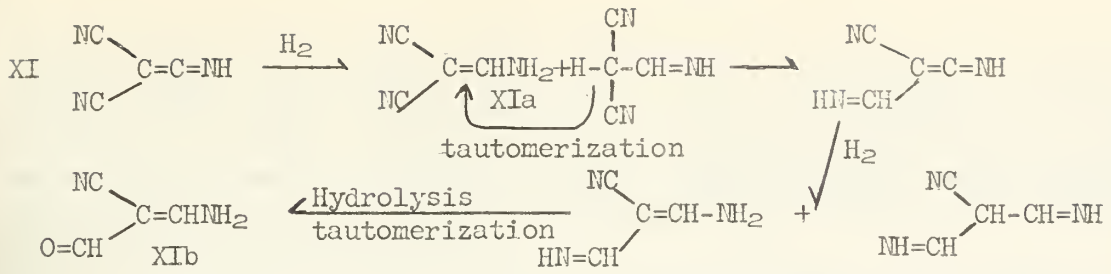
Z=OR, Cl, Br

IX 

The suggestion of addition across the C-N double bond is in disagreement with previous reports of reactions of ketenimines.[1,15] Stevens and French reported Scheme X as proof that methanol adds across the C-C double bond of ketenimines. Unfortunately they do not seem to have considered the possibility of tautomerism of the addition product, and they did not obtain an IR spectrum of the addition product.[1,15]

X 

As proof that the addition of acids, alcohols (VIII) and amines (IX) takes place across the C-N double bond, Trofimenko and co-workers report that infrared spectra of the addition products show NH_2 bands.[12] Trofimenko has studied the catalytic hydrogenation of aqueous ethereal solutions of cyanoform using palladium on charcoal as catalysis. He observed two products, 3-amino-2-cyanoacrylonitrile (XIa) and 3-amino-2-cyanoacrolein (XIb). Mechanism XI was proposed.



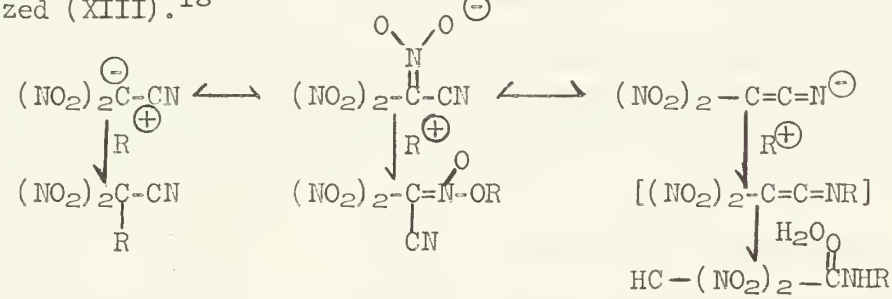
The potassium salt was inert under the hydrogenation conditions.[16]

Recently Parker and co-workers synthesized dinitroacetonitrile. This compound would be expected to have many properties in common with cyanoform, for they both contain a cyanide group attached to a carbon bearing two electronegative groups. Dinitrocyanomethide salts were formed from the reaction of trinitroacetonitrile with hydrogen sulfide (XII).[17]

XII $C(NO_2)_3CN + 4H_2S \longrightarrow NH_4^{\oplus}\ C(NO_2)_2CN^{\ominus} + 4S + 2H_2O$

It was observed that allyl and t-Butyl halides alkylated the silver salt of dinitroacetonitrile on carbon, nitrogen, and oxygen suggesting that the anion is highly resonance stabilized (XIII).[18]

XIII



Certain acetonitriles containing sulphonyl substituents react through nitrogen. Only the N-methyl compound results when 2,2-bis(methylsulphonyl)vinylideneamine is allowed to react with diazomethane while 2-methylsulphonyl-2-phenylsulphonylvinylideneamine gives a mixture of N- and C-alkylated products (XIV). Less acidic nitriles undergo only C-methylation.[19]

XIV $(\phi SO_2)(CH_3SO_2)CHCN \xrightarrow{CN_2N_2} (\phi SO_2)(CH_3SO_2)-C=C=NCH_3 + (\phi SO_2)(CH_3SO_2)(CH_3)-CCN$

There are also examples of N-alkylation of acetonitriles which are not substituted with strong electron withdrawing groups. Newman and co-workers have observed steric shielding influences the position of alkylation in nitriles. They observed that in the presence of strong base those nitriles which had a six number * of twelve or greater undergo both C- and N-alkylation with i-propyliodide. With t-butyl-i-propylacetonitrile, which has a six number of 15, only N-alkylation was observed.[20] Prober has observed that in the silico-alkylation of acetonitrile a major product is a ketenimine (XVa). The ketenimine is not the thermodynamically favored product and it will rearrange when heated in water to give the bis-substituted nitrile (XVb).

$[(CH_3)_3Si]_2CHCN$ XVb $\qquad$ $(CH_3)_3SiCH=C=N-Si(CH_3)_3$ XVa

It was also observed that benzylcyanide reacts with trimethylchlorosilane in the presence of base to form a mixture of the C- and the N-silico-alkylation products.[21]

We have seen that ketenimines can be obtained by tautomerization of nitriles and by N-alkylation of nitriles. Other methods of preparation of ketenimines which have previously been reviewed[1] are listed below:

1.) $Ar_3P=C(Ar)_2 + ArN=C=O \longrightarrow Ar_2C=C=NAr + Ar_3P=O$
2.) $R_3P=NR + R_2C=C=O \longrightarrow R_3P=O + R_2C=C=NR$
3.) $Ar_2C(Cl)C(Cl)=NAr + NaI \longrightarrow Ar_2C=C=NAr$
4.) $(CH_3)_2-CHCONHAr + PCl_5 \longrightarrow (CH_3)_2CHC(Cl)=NAr \xrightarrow{Et_3N} (CH_3)_2C=C=NAr$

* The rule of six: "In reactions involving addition to an unsaturated function containing a double bond, the greater the number of atoms in the six position, the greater will be the steric effect." The number of atoms in the six position is called the six number.[25c]

It has long been recognized that ketenimines can be produced by the reaction of phosphinimines with ketenes. This method has a disadvantage in that phosphinimines are not always easily synthesized and at times the isolation of the product presents a problem.[1] A method similar to the use of phosphinimines has been reported by Wadsworth and Emmons. In this procedure dialkyl phosphoramidate anions are used XVI). This procedure is simplier than one using phosphinimines, but to be used the substrate must be stable to base.[22]

XVI $(EtO)_2\overset{O}{\overset{\uparrow}{P}}Cl + RNH_2 \longrightarrow (EtO)_2\overset{O}{\overset{\uparrow}{P}}NHR \xrightarrow{NaH} (EtO)_2\overset{O}{\overset{\uparrow}{P}}(\ominus)NR \xrightarrow{R_2C=C=O} RN=C=CR_2$

Another method of synthesizing ketenimines has been found by Stevens and Singhal. This method is similar to a method of preparing nitriles by the dehydration of unsubstituted amides.[23] The authors used N-substituted amides and observed in many cases ketenimines could be obtained in good yield upon dehydration with phosphorous pentoxide. This reaction was found to work for amides with either aryl or alkyl groups on both the nitrogen and the carbon, in most cases giving ketenimines in better than 50% yield. The reaction would not go if the nitrogen contained a p-nitrophenyl group and, in the case of α(diphenyl)-N-t-Butyl-acetamide, a nitrile and not a ketenimine was formed.[24]

Talat-Erben and Bywater while studying the thermal decomposition of 2,2'-azo-bis-isobutyro-nitrile (XVII) observed that by extracting the reaction mixture from kinetic studies they were able to isolate two dipeptides, XVIIIa and XVIIIb. They suggested that these peptides arose from the reaction of the ketenimine XIX with water.

XVII $(CH_3)_2\overset{CN}{\overset{|}{C}}-N=N-\overset{CN}{\overset{|}{C}}(CH_3)_2$

XVIIIa $(CH_3)_2CHC(=O)NHC(CH_3)_2C(=O)OH$

XVIIIb $(CH_3)_2CHCNHC(CH_3)_2\overset{O}{\overset{\|}{C}}NH_2$

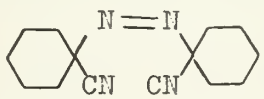
XIX $(CH_3)_2C=C=N-C-(CH_3)_2-CN$

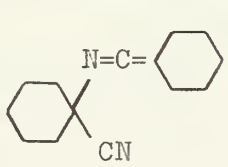
As additional evidence for the formation of the ketenimine, XIX, the authors report that the reaction mixture had an IR absorption at 2005 cm^{-1}. An absorption in this region had previously been assigned to the ketenimine structure.[1] As explanation of the ketenimine formation, it has been suggested that the resonance stabilized radical can either react through the carbon or the nitrogen.

XX $[(CH_3)_2\dot{C}CN \leftrightarrow (CH_3)_2C=C=N\cdot]$

XXI $(CH_3)_2\overset{CN}{\overset{|}{C}}-\overset{CN}{\overset{|}{C}}(CH_3)_2$

It was estimated that about 1/3 of the radicals reacted through the nitrogen.[25] Additional proof for the formation of an intermediate ketenimine was obtained by observing the OD at 320 mμ.[26] The study of the ketenimine formed is complicated by the fact that it isomerizes to give tetramethylsuccinonitrile (XXI) which is also obtained directly from 2,2'-azo-bis-isobutyronitrile (XVII). Hammond and co-workers were able to isolate the ketenimine XIX by thermally decomposing the azo compound in petroleum ether in which the reactant XVII and other product (XXI) were slightly soluble and could be removed from the ketenimine (XIX) by filtration. The ketenimine was found to react with water, I_2, Br_2. and BuSH. Hammond and co-workers have suggested that the ketenimine (XIX) is formed in a solvent "cage" since the yield is not greatly affected by radical scavengers.[27]

XXII 

XXIII 

Later Hammond and co-workers used this method of ketenimine preparation for the synthesis of N-(1-cyanocyclohexyl)-pentamethylene ketenimine XXIII from 1,1'-azo-bis-cyanocyclohexane (XXII).[28] Smith, Sheats and Miller observed that for the synthesis of ketenimine (XIX) photolysis of 2,2'-azo-bis-isobutyronitrile has an advantage over pyrolysis. The ketenimine is stable under the photolytic, but not the pyrolytic condition.[29]

Considering the information obtained by Talat-Erben and Bywater[25,26] and by Hammond and co-workers[27] showing that radicals α to a nitrile group can react through the nitrogen, and considering the steric effect on determination of the location of attack, it is not too surprising that when methylacrylonitrile undergoes free radical polymerization, some ketenimine structure is formed. N. Grassie and I. C. McNeill have observed that polymethylacrylonitrile contains an IR band at 2012 cm^{-1} which they have assigned to a ketenimine structure.

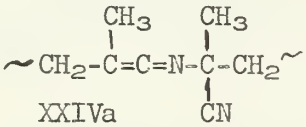
There has been much interest in the formation of ketenimine linkages in polymethylacrylonitrile. These polymers are invariably less stable than one would expect. One reason is the incorporation of monomer units in unusual configurations.

Upon heating the polymer at 140°C for 15 minutes, the 2012 cm^{-1} band disappears; there is a 30% decline in average molecular weight.[30] The kinetics of the loss of the ketenimine units in the polymer have been studied by observing the loss of absorption at 2012 cm^{-1}. The reaction was found to be second order. The authors suggested that the ketenimine moity dimerizes in the rate determining step and then rapidly decomposes. Upon observing that the degree of incorporation was independent of the rate of initiation, it was suggested that the ketenimine structures are formed in a termination process. This suggests that the ketenimine radical is unreactive and has little tendency to add monomer, but must be destroyed by another radical.[31] Reactions of the ketenimine moity of the polymer with water, chlorine, hydrogen sulfide and methanol-sodium methoxide were studied by observing the IR spectra before and after reaction. See Table 2.[32]

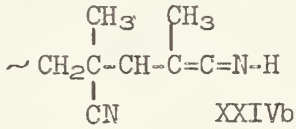
TABLE 2

Reagent	2012 cm^{-1} peak	New Absorption
H_2O	Reduced	1680, 1620
Cl_2	Absent	1680
MeOH	Unaffected	none
MeOH, MeONa	Absent	1700-1570
H_2S	Absent	1620

A theoretical treatment undertaken also indicated that the ketenimine structure formed during termination but not propagation. It was suggested that the ketenimine structure is formed by combination to give XXIVa and not by disproportion to give XXIVb. The reason for choosing combination rather than disproportionation as the method of formation of ketenimine structures is that most ketenimines of type XXIVb are unstable. More over, loss of the ketenimine XXIVb cannot account for the 30% decrease in molecular weight.



XXIVa



XXIVb

From a knowledge of decrease in molecular weight when the ketenimine structure is destroyed the number of radicals in the ketenimine form was estimated.

M_o = initial molecular weight n = number of scissions/molecule

M_d = final molecular weight

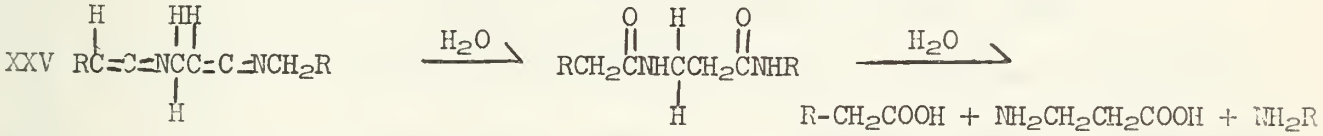
$M_d = \frac{M_o}{(n+1)}$ for a 30% decrease in molecular weight $n = \frac{M_o - M_d}{M_d} \simeq .4$

since n links ⟶ 2n radicals

The number of radicals in the ketenimine form was between 2n and n; this means 40-80% of the polymer chains were terminated through nitrogen.[32] Talat-Erben et al. estimated that in 2,2'-azo-bis-isobuteronitrile, 1/2 of the radicals reacted through nitrogen.[41] While it appears that no evidence has been published indicating that acrylonitrile polymerizers with any ketenimine type structure under normal conditions, it has been found that X-ray irradiation of pure liquid acrylonitrile

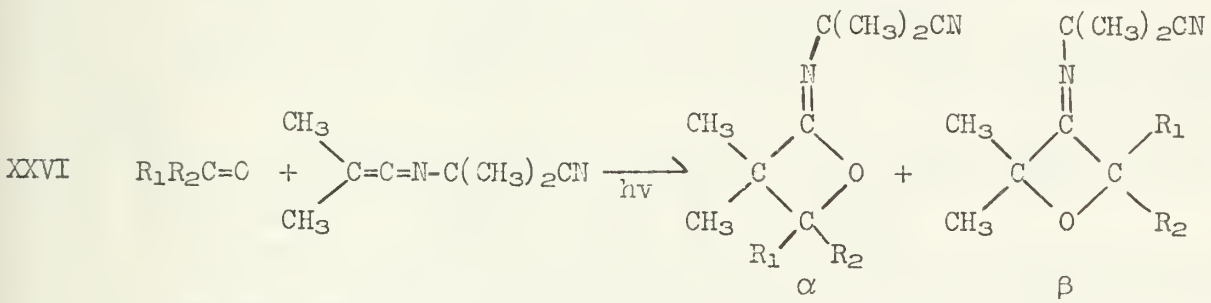
at 78.5°C leads to a polymer with a sharp band at 2030 cm^{-1}. As evidence that this is a ketenimine structure it is reported that in aquous hydrochloric acid this band is replaced by two others (1675 cm^{-1} and 1525 cm^{-1}) which are assigned to a mono substituted amide. It is claimed that the ketenimine band is about 1/3 the intensity of the nitrile band, and stated that this indicates that approximately 1/3 of the monomers react through nitrogen.[33] No significant change is noted in the IR spectra of polyacrylonitrile after X-ray irradiation.[34]

Tsuda reports that gamma ray irradiation of bulk acrylo nitrile at -78.5°C leads to a polymer containing ketenimine structures. It is interesting to note that the polymers from bulk gamma ray irradiation polymerization at -196°C and at 17°C do not contain a 2030 cm^{-1} IR band, nor does the polymer from gamma ray irradiation of acrylonitrile in triethylamine at -78.5°C contain any ketenimine structure.[35] (In the cases where the polyacrylonitrile contains no ketenimine linkages it is believed anion polymerization took place.) Deichert and Tobin observed that polymerization of acrylonitrile initiated by a 20,000v 60 cycle electric discharge leads to a product which shows both nitrile (2240 cm^{-1}) and ketenimine bands (2019 cm^{-1}) in the IR.[36] Levine and Harris observed that electron discharge initiated polymerization of acrylonitrile, in air at -78.5°C, leads to a polymer which contains 3-5% of the ketenimine structure. Hydrolysis of the polymer gave β-alanine as one product, XXV.



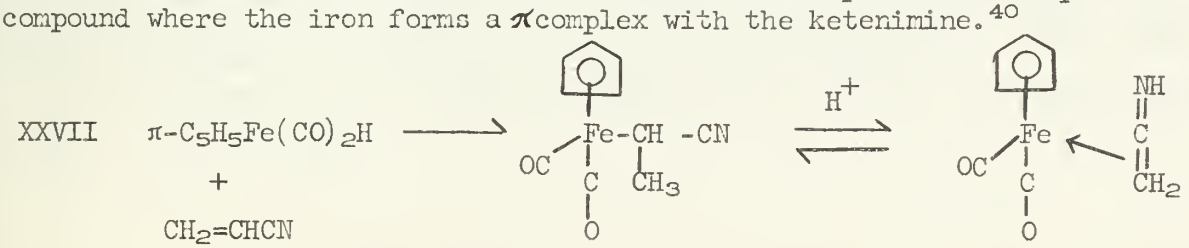
In order for β-alanine to appear there must be two adjacent head to tail ketenimine structures. This structure feature could not be caused by the combination of two radicals (termination step): therefore, it can be concluded that in this polymerization the 1,4 reaction of acrylonitrile occurs in another manner.[37] It is interesting to note that this differs from peroxide initiated polymerization of methylacrylonitrile where the ketenimine structure was formed in a termination step.

Singer and Bartlett have observed the photocycloaddition of aromatic aldehydes and ketones across the carbon-carbon double bond of dimethyl-N-(2-cyano-2-propyl)-ketenimine to give iminooxetanes (XXVI). The β adducts were isolated by Florisil chromatography while the α adducts were hydrolyzed to amides on Florisil.[38]



Cremlyn, Kenner and Todd used ketenimines as a reagent for the condensation of phosphates to pyrophosphates, but they note no advantages over carbodi-imides.[39]

Ariyaratne and Green observed that acrylonitrile reacted with π-$C_5H_5Fe(CO)_2H$ adding across the carbon-carbon double bond. This compound is in equilibrium with a compound where the iron forms a π complex with the ketenimine.[40]



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TRIPLET ENERGY TRANSFER: A MECHANISM FOR PHOTOSENSITIZATION IN SOLUTION

Reported by James E. Gano February 18, 1965

Various reviews and an increasing number of articles in the recent literature show the interest that organic chemists are taking in photosensitized reactions.[1,2,3] This interest has ranged from a purely synthetic standpoint to the elucidation of reaction mechanisms. The purpose of this seminar is to critically evaluate postulated mechanisms for triplet energy transfer.

A number of reviews have been written on triplet energy transfer in solution.[4,5,6] Although this phenomenon has been extensively studied in solid solutions at liquid air temperature, this work will be covered here only to the extent to which it is needed to help explain triplet energy transfer as it occurs in solution at room temperature.[4,7]

A general knowledge of the nomenclature and phenomena involved in photochemical studies will be assumed although a brief summary follows. More extensive discussions of the triplet state and the electronic processes involved are available.[2,3,8,9] The normal ground state of most molecules is that of a singlet, designated $^1\Gamma_0$. This means that all electrons in the molecule have paired spins. Absorption of a quantum of light promotes the molecule to an excited state, $^1\Gamma_n$. The paths the excited singlet state can follow are shown in Figure I. Note especially the formation of excited triplet states, $^3\Gamma_n$, by intersystem crossing. These triplet states, which are characterized by their unpaired electrons with parallel spins, are the energy donor molecules in triplet energy transfer.

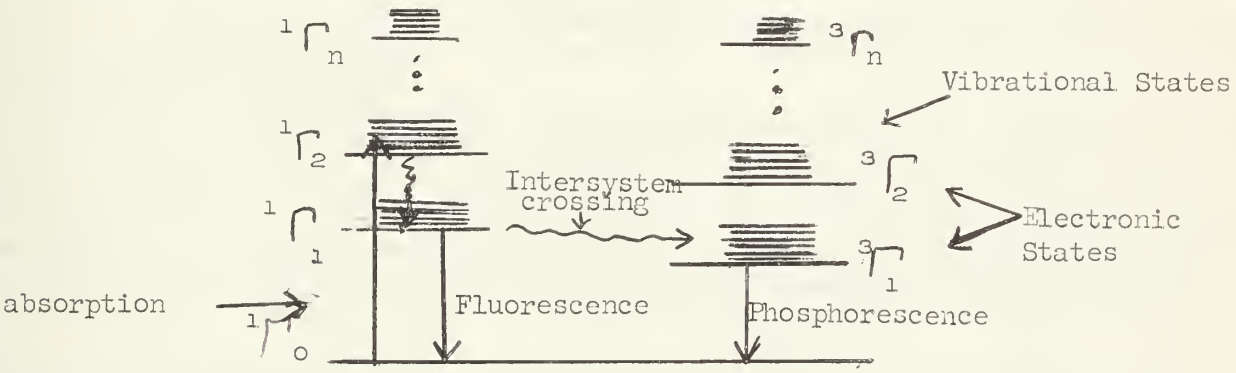


Figure I. A Jablonski diagram of energy transitions in a hypothetical molecule.

It should also be noted that fluorescence and phosphorescence are defined in this diagram by the states between which the transitions occur and not by the time interval between absorption and emission. Definitions of most of the symbols to be used are given below:

τ time required for some observable phenomenon to be half completed or half extinguished as pertains to observable triplet state emission (phosphorescence).

$^1\Gamma_n$ the n^{th} single state of a molecule

$^3\Gamma_n$ the n^{th} triplet state of a molecule

$^3\Gamma_1$ the lowest observable triplet state of a molecule.

History. Triplet energy transfer was first observed in a solid solution at liquid air temperature by Ermolaev and Terenin.[10] They reported that various compounds emitted characteristic phosphorescent spectra when irradiated with light which they could not absorb if they were mixed with certain other compounds that could absorb the light. For example, napthalene (10^{-3}-10^{-2}M) when irradiated at 3663 Å in an ethanol matrix emitted little or no light. The addition of benzaldehyde to the matrix, however, resulted in the simultaneous emission of the fluorescent spectrum of benzaldehyde and the phosphorescent spectrum of napthalene. The authors noted the relative energy levels of the benzaldehyde (25200 $cm.^{-1}$) and napthalene (21,300 cm^{-1}) triplet states and proposed that their observations were due to the transfer of energy from the lowest excited triplet state of benzaldehyde to napthalene causing excitation to its lowest triplet state. This is shown diagrammatically below.

$$^3\Gamma_1(\text{benz}) + {}^1\Gamma_0(\text{nap}) \longrightarrow {}^1\Gamma_0(\text{benz}) + {}^3\Gamma_n(\text{nap})$$

The same phenomenon, occuring in solution at <u>room</u> temperature, was soon thereafter reported by Bäckström and Sandros.[11,12] They found that the phosphorescence of biacetyl in degassed benzene solutions could be quenched by the addition of various alcohols, amines, phenols, and aromatic hydrocarbons. Flash techniques were used to measure the half life of the biacetyl phosphorescence as a function of quencher concentration. These values, substituted into the Stern-Volmer equation shown below, give the rate constants for quenching listed in Table I.

$$\frac{1}{\tau} = \frac{1}{\tau_0} - k_q C$$

<u>The Stern-Volmer Equation</u>. τ is the half life of the biacetyl triplet state emission with quencher present. τ_0 is the half life of biacetyl triplet state emssion alone. C is the concentration of quencher.
The concentration of quencher was varied so as to range τ from τ_0 to $\tau_0/10$. There

Table I. Quenching rates in benzene at 20°C.[12]

Methanol	2.6×10^2	Nitrobenzene	4.4×10^4
Benzyl Alcohol	6.9×10^3	1,3,5,-Trinitrobenzene	1.1×10^6
Phenol	8.9×10^7	Naphthalene	3.8×10^3
Hydroquinone	5.3×10^9	Anthracene	8.1×10^9
Diphenylamine	6.8×10^9	Pyrene	7.5×10^9
Perchlorethylene	3.5×10^4	1,2-Benzanthracene	3.8×10^9 *$3\pm2\times10^9$

was, however, difficulty in obtaining reproducable values with benzene obtained from different sources but purified in the same manner, which suggests these rates might not be as accurate as indicated.

Bäckström and Sandros recognized that the quenching action of compounds such as alcohols, amines, and phenols was by a chemical reaction, namely loss of a proton to a biacetyl molecule in an excited triplet state. The rates of quenching by aromatic hydrocarbons, however, were much faster, approaching the rates of diffusion. These hydrocarbons did not possess easily abstractible protons. It was postulated that these compounds quenched by a triplet energy transfer mechanism similar to that proposed by Emolaev and Terenin for sensitized phosphorescence at liquid air temperatures.

<u>Confirmation of an Energy Transfer and Its Properties</u>. Many experiments at room temperature and at 77°K[13] show conclusively that a physical transfer of energy can occur between a molecule excited to a triplet state and a molecule in the ground singlet state resulting in the excitation of the acceptor molecule to a triplet state. Porter and Wilkinson irradiated solutions at 20-25°C with a photolysis flash lamp and then measured the rates of decay of the triplet states of the donor and acceptor with a spectro-flash lamp.[14] A typical example was the sensitized phophorescence of naphthalene (2.3×10^{-3}M) by phenanthrene (6.9×10^{-3}M) in hexane solution. Note this shows that the triplet energy transfer process does not require the participation of carbonyl containing compounds. The decay constants, k_1, were determined separately for solutions of donor and of acceptor. Then donor and acceptor were mixed in a hexane solution and flash photolyzed. The light, before entering the solution, was allowed to pass through a concentrated solution of naphthalene. This insured that the naphthalene in solution with benzophenone could not be excited by <u>direct</u> absorption of the incident radiation. The triplet state emission of the donor was completely suppressed by energy transfer to the acceptor and only the absorption spectra of the triplet state of the energy acceptor was seen. The following rate law was proposed to account for the observed rate of triplet state decay of the donor in the presence of the acceptor. The $k_2(T)^2$ term was ignored because of the low concentration of triplet state molecules. Using the values of k_1 determined previously, Porter and Wilkinson determined k_q in this case to be $2.9\pm0.9\times10^6$.

$$\frac{-d(T)}{d(t)} = k_1(T) + k_2(T)^2 + k_q(Q)(T)$$

* From Porter and Wilkinson for comparison.[14]

Simultaneously Bäckström and Sandros[15] confirmed the existence of triplet energy transfer using different techniques. They recorded the luminescent spectra of biacetyl and other acceptors produced under the following conditions:

a) Direct irradiation at 3660 Å in benzene solution.
b) Direct irradiation at 3660 Å in benzene solution with pyrene added to quench all phosphorescent emission.
c) Direct irradiation at 3660 Å in benzene with a sufficient concentration of benzophenone to absorb 95% of the incident radiation.

Since benzophenone shows no fluorescence or phosphorescence in solution at room temperature, all emission observed was from the energy acceptor. The spectra obtained are reproduced in Figure II.

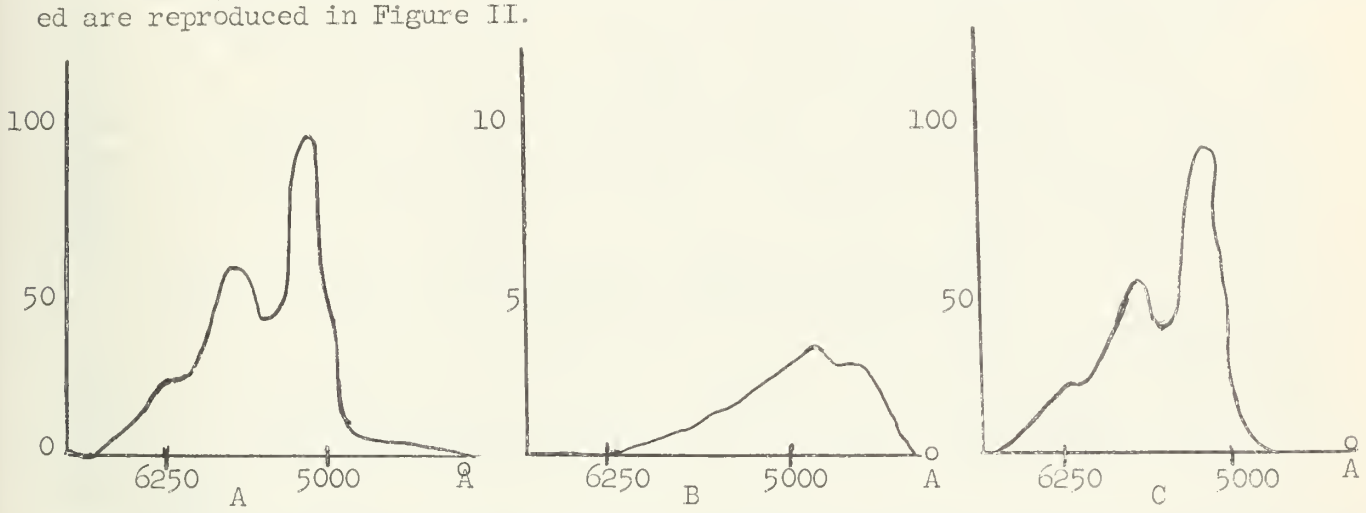


Figure II. (A) Luminescint spectra of biacetyl irradiated under conditions a). (B) Under conditions b). (C) Under conditions c).[15]

The authors noted that only the phosphorescent portion of biacetyl emission was visible in Figure II (C) indicating that energy was only being transferred from the triplet state of the donor molecule. Other workers conclude that benzophenone cannot transfer energy from an excited singlet state because, since it shows no fluorescence, the intersystem crossing in the excited molecule to the triplet level is almost complete.[16] As added proof of triplet energy transfer, Bäckström and Sandros compared quantitatively the luminescence of a 3.0×10^{-3}M biacetyl solution in benzene alone and with benzophenone added. After the addition of the donor, a ninefold increase in luminescence intensity was observed.

Farmer and coworkers,[17] using e.s.r. techniques, recently provided more evidence for triplet energy transfer. They reported observing the naphthalene triplet spectrum when an E.P.A. glass containing naphthalene and benzophene was irradiated at 3600 Å. Only benzophenone absorbs light significantly at this frequency. The ketyl radical is formed very quickly under these conditions by proton abstraction; therefore, its spectrum was also observed. Although the results seem to be consistent in every way with those obtained in situations where no free radical is formed, an energy donor without this added complication would have been more appropriate.

The extensive work by Bäckström and Sandros and Porter and Wilkinson showed that organic compounds can be divided into three classes according to their ability to accept triplet state energy. This classification depends upon the relative energy levels of the triplet states of donor and acceptor. Where the triplet level of the acceptor is far above that of the donor, evergy transfer is an endothermic process and is not expected to occur.[14]

Bäckström and Sandros[18] have proposed that where the triplet level of the acceptor is only slightly above that of the donor, energy transfer can occur at room temperature because the donor can transfer energy from a higher vibrational level of its triplet state to a lower vibrational level of the triplet state of the acceptor. See Figure I for the relation of vibrational levels to electronic levels. Increasing the concentration of acceptor will lower the efficiency of the overall

process because the transfer of energy back to the original donor will become more probable. The rate of energy transfer observed with these acceptors is much slower than diffusion controlled even in very viscous solvents where the diffusion rate is much less.[14] ~~Energy transfer of this type has been used by Hammond and co-workers[19] to explain why o-hydroxybenzoyl compounds improve the light stability of commercial polymers.~~

When the triplet state energy level of the acceptor is much below that of the donor, the rate of energy transfer has been shown to be diffusion controlled. Hammond and others have demonstrated this in competition experiments.[20,21] By letting both benzhydrol and various triplet energy acceptors compete for excited donor molecules, in this case benzophenone, Hammond found that the rate of triplet energy transfer was not only about 800 times greater than proton abstraction, but also, that various energy acceptors, such as naphthalene, 1-naphthaldehyde, 2-acetonaphthone, piperylene and cyclooctatetraene, competed with similar efficiencies. From this observation he concluded that the limiting process must be the same for all energy acceptors studied. The one thing they had in common was their approximate rates of diffusion. As mentioned earlier, Bäckström and Sandros and Porter and Wilkinson came to this same conclusion by comparing the rates of energy transfer found experimentally with those predicted by the Debye equation for a diffusion controlled process.[22]

There have been five mechanisms proposed by which sensitized phosphorescence or transfer of triplet state energy can occur. They include the formation of a complex between the donor and acceptor, emission of a photon by the donor and its subsequent absorption by the acceptor, transfer of excited singlet state energy followed by intersystem crossing, transfer of triplet state energy by way of solvent molecules, and direct triplet energy transfer. These will be discussed individually.

Complex Formation. Often the ultraviolet spectrum of the solution containing thedonor and acceptor is exactly what one would get by superimposing the separate spectra of the donor and acceptor. If a complex formed, one would expect a change in the spectra of the mixture.[13,14] No spectral change was observed in the cases of triplet energy transfer reported.

Eisenthal and Murashige[23], suspecting the formation of a weak complex at the liquid air temperatures used in much of the earlier work, polymerized methylmethacrylate monomer containing benzophenone (5×10^{-2}M) and naphthalene (0.2-0.05M) at temperatures above room temperature. The intensity of the benzophenone phosphorescence was observed to decrease and naphthalene phosphorescence appeared when the polymer was irradiated at 3650 Å at room temperature, demonstrating a transfer of energy. A polymer containing only naphthalene showed no emission under these conditions. This indicated that a complex was not necessary for sensitized phosphorescence to occur. As was noted, the possibility of incomplete solubility in the monomer resulting in molecular aggregates of solute molecules was not ruled out. Very recently Kusuhara and Hardwick[24] carried out a similar experiment and obtained different results. They used coronene (2×10^{-4}M) as the energy donor, anthracene (1×10^{-4}M) as the acceptor and triplet-triplet absorption spectra to detect energy transfer. In bromobenzene solution, the expected sensitized triplet state of anthracene was observed; however, the triplet state was not observed when the solutes were present in a methylmethacrylate polymer. This was given as evidence that triplet-triplet energy transfer occurs by a collision process which could not occur in the rigid methylmethacrylate polymer. No note was taken of Eisenthal and Murashige's results. A likely explaination, in view of the previous experiment, is that energy transfer did occur but at a much reduced rate because of the high "solvent" viscosity. Note the relative concentrations.

Eisenthal and Siegel,[25] studying the rate of decay of the donor and acceptor triplet states by means of e.s.r., found that the life times of the triplet states of carbazole (donor) and biphenyl (acceptor) in a glass at 77°K were not affected by each others presence, indicating no interaction (i.e. no complex formation).

They also found that no change in transfer efficiency was observed if the solutions were allowed to equilibrate at 203°K or 248°K before quickly cooling to 77°K. This showed, assuming the equilibrium concentration of complex to be temperature dependent and the concentration of complex at 77°K to be similar to the equilibrium concentration attained at the higher temperature, that no complex participates in the energy transfer. Porter and Wilkinson[14] showed that when an energy acceptor (iodonaphthalene) was present in a concentration expected to lead to a 2% decrease in the phosphorescence of the donor (phenanthrene), a five fold decrease was observed. This indicates that some process other than complex formation is occurring.

Schenck has studied a series of photosensitized reactions including dimerizations across double bonds, oxidations and addition reactions.[1,26,27] Typical energy donors were rose bengal, eosin and benzophenone. He concluded that sensitized photoreactions proceed by a mechanism incorporating either a proton abstraction step or the formation of a short-lived photoadduct biradical. The first mechanism is generally accepted and was mentioned earlier with reference to work by Bäckström and Sandros.[11] The second and more pertinent mechanism is shown below. The overall reaction is the formation of XY by an addition reaction.

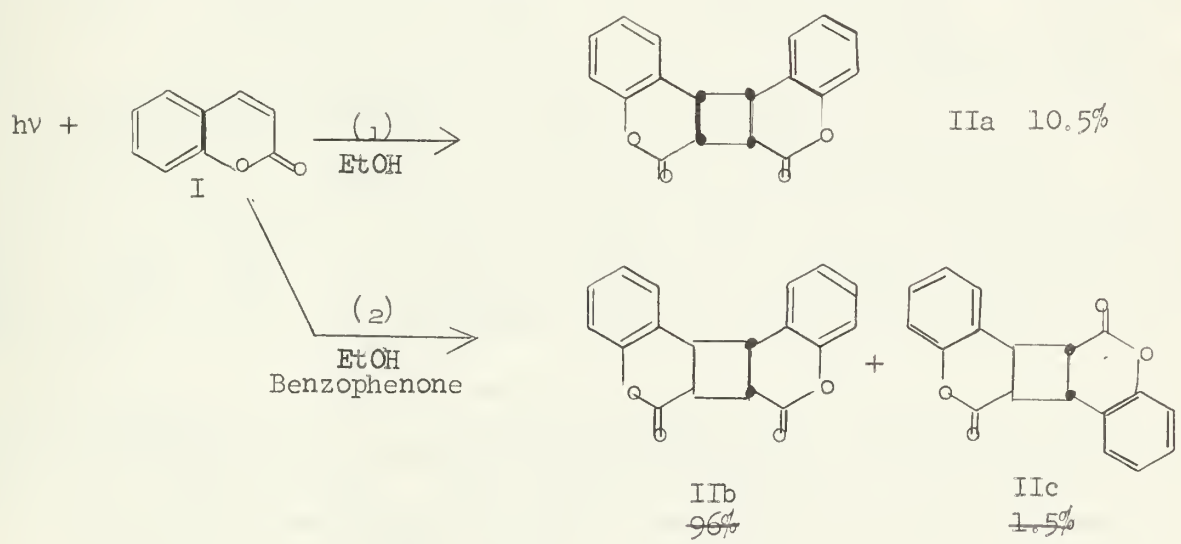
$$\text{Sens} + h\nu \rightarrow {}^{\cdot}\text{Sens}^{\cdot}{}^{\text{Rad}} \xrightarrow{+X} {}^{\cdot}\text{Sens}\cdots\text{X}^{\cdot}{}^{\text{Rad}} \xrightarrow{+Y} \text{Sens} + \text{X-Y}$$

$$\downarrow \text{Sens} \qquad\qquad \downarrow \text{Sens} + \text{X}$$

Schenck's mechanism for photosensitization. ${}^{\cdot}\text{Sens}^{\cdot}{}^{\text{Rad}}$ is presumably the triplet state of the sensitizer.

The evidence for this mechanism[28] rests on the observation of different e.s.r. spectra when methanol solutions of rose bengal mixed with various solutes, such as coumarin or naphthalene, were irradiated with light of wavelengths > 5000 Å. These spectra were attributed to the photoadduct biradical, $\cdot\text{Sens}\cdot\cdot\text{X}^{\text{Rad}}$. The explaination of the observed spectra seemed more complicated than should have been necessary and the possibility of complex formation before excitation was not discussed. Also, the possibility of energy transfer by a collision process, thus yielding e.s.r. spectra of the excited acceptors, was not suggested.

Hammond has recently successfully attacked one example given by Schenck for his mechanism.[29] The dimerization of coumarin by direct irradiation and photosensitization with benzophenone leads to different products as shown below.



Schenck and co-workers proposed that excited triplet state coumarin and the photoadduct biradical were the reaction intermediates in reaction (1) and (2) respectively, thus explaining the different products.[26] Among other things, Hammond found that benzophenone controls the reaction path even if all of the incident light is absorbed by the coumarin. He concluded that the excited coumarin in this case transfers energy by singlet-singlet transfer to benzophenone. The benzophenone undergoes intersystem crossing and excites the coumarin by triplet-triplet energy transfer. The excited coumarin triplet then undergoes reaction to form IIb and IIc. Reaction (1)is believed to result from an encounter between excited coumarin singlets and ground state molecules. At high concentrations, there is a fair probability for such collisions.

In summary, evidence has been presented to show that complex formation is not required for triplet energy transfer to occur. Further study is needed before Schenck's mechanism can be confirmed or rejected in the other cases noted.

Emission and Reabsorption. The possibility of an excited donor molecule emitting phosphorescent radiation which is then absorbed by the acceptor has been attacked from many sides. Porter and Wilkinson[14] noted that the fraction of molecules in the triplet state that decay by a radiative process at room temperature is usually very small; therefore, any process resulting from this must be minor. This is not the case in sensitized phosphorescence where quantum yields are often high. Ermolaev and Terenin have shown such an explanation to be impossible in many cases of sensitized phosphorescence because the acceptors do not possess absorption bands in the donors' emission region.[13] It can be concluded with a fair degree of certainty that sensitized phosphorescence is not an emission-reabsorption process. The feasibility of the process, however, forbids a denial of its eventual demonstration in special cases.

Singlet Energy Transfer Followed by Intersystem Crossing. An obvious explanation

$$^1\lceil_1\rceil\,(\text{Donor}) + {}^1\lceil_0\rceil\,(\text{Acceptor}) \rightarrow {}^1\lceil_0\rceil\,(\text{Donor}) + {}^1\lceil_n\rceil\,(\text{Acceptor})$$

$$^1\lceil_n\rceil\,(\text{Acceptor}) \rightarrow {}^3\lceil_n\rceil\,(\text{Acceptor})$$

for sensitized phosphorescence is the transfer of energy from a donor molecule in an excited singlet state to an acceptor molecule in the ground singlet state. This could result in the acceptor's excitation to a higher singlet state followed by intersystem crossing to a triplet state. This is shown above diagrammatically. The transfer of singlet state energy is a well known phenomenon. A theory has been worked out by Fõrster and others that correlates well with experimental data.[30] The electronic interaction that occurs in singlet-singlet energy transfer (called dipole-dipole resonance or inductive resonance)requires the overlap of the emission band of the donor and the absorption band of the acceptor. Therefore, its occurrance can be predicted. According to Wilkinson and Dubois,[31,32] the path a molecule follows once it is in an excited singlet state should not be strongly dependent on the manner in which it attained that state. If singlet-singlet energy transfer were to occur and be followed by intersystem crossing and sensitized phosphorescence, the emission spectra of the sensitized molecule should be very similar, to its emission spectra resulting from direct absorption of U.V. radiation.

Wilkinson and Dubois[31,32] used this proposal to prove that sensitized phosphorescence can occur by the mechanism mentioned above. Biacetyl, which gives directly observable fluorescence and phosphorescence at room temperature, was used as the energy acceptor. When benzene or toluene were used as the sensitizers in aerated or deaerated hexane solutions, the P/F ratio (within 10%) was found to be independent of donor concentration although the luminescent intensity increased. Furthermore, the sensitized luminescent spectrum was identical to that resulting from direct absorption of light by biacetyl. Wilkinson and Dubois concluded that singlet-singlet energy transfer with subsequent intersystem crossing was the mechanism of sensitized phosphorescence and fluorescence in the case of biacetyl and that triplet-triplet energy transfer did not occur because

the lifetime of the benzene triplet state was too short. Recently, Lipsky,[33] comparing the ratio of biacetyl phosphorescence to benzene fluorescence as a function of benzene concentration, showed that triplet-triplet energy transfer actually does occur in this case. Possibly Wilkinson and Dubois failed to observe this due to a small amount of residual oxygen.[6] The important point is that sensitized phosphorescence can occur by this mechanism even though this is a special case.

In many instances simultaneous sensitization of fluorescence and phosphorescence does not occur (See Figure II C as an example).

Transfer of Triplet State Energy via Solvent Molecules. Although the participation of solvent molecules in triplet-triplet energy transfer has been established in crystalline systems,[4] no direct evidence has been found for its occurance in solutions. On the contrary, Siegel,[34] in some recent work using e.s.r. techniques, found no solvent effects for triplet-triplet energy transfer at 77° K. Various alcoholic, aromatic, and ether solvent mixtures were used, thus indicating the solvent did not participate in energy transfer.

Transfer of Triplet State Energy Directly. Having considered the alternate mechanisms for sensitized phosphorescence and found that they do not sufficiently explain the experimental evidence, only a direct transfer of triplet state energy during bimolecular collision remains. This process, originally proposed by Ermolaev and Terenin for sensatized phosphorescence at low temperatures, is shown in Figure III.

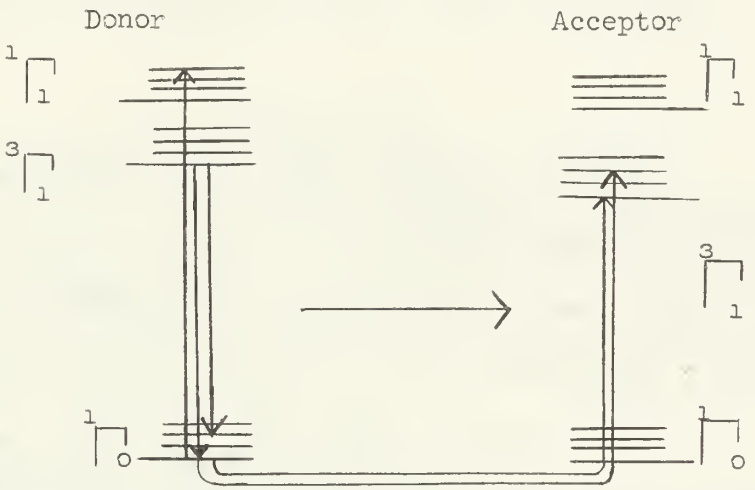


Figure III. A diagrammatic representation of triplet energy transfer as proposed by Terenin and Ermolaev.[35]

A considerable volume of experimental evidence has been put forward by Ermolaev and Terenin to demonstrate that triplet energy transfer, at least at 77°K., is an exchange resonance phenomenon.[7,35,36,37] Even though an extensive discussion at this point is beyond the scope of this seminar, enough will be said to give an organic chemist an intuitive feeling for the phenomenon. A more extensive discussion of this and other resonance interactions can be found in an article by Dexter[38] and in a recent review.[6] Altogether, Ermolaev and Terenin note five theoretical interactions between two molecules that could be used to explain triplet energy transfer. Some of these interactions, such as dipole-dipole resonance (mentioned previously in connection with singlet-singlet energy transfer), can occur while the interacting molecules are 50 to 100Å apart. An exchange resonance interaction, in contrast, occurs when the electron clouds of the two interacting molecules overlap,[38] thus requiring a molecular collision. This is consistant with experimental results for triplet-triplet energy transfer.[14,35]

In a dipole-dipole resonance interaction, the spins of the donor and acceptor must be the same. For an exchange resonance interaction however,[38] the only

requirement is that the total multiplicity before and after the energy transfer is the same. This requirement is fulfilled by triplet energy transfer.

Ermolaev and Terenin[35] found that the donor phosphorescence yield, n, at 77°K. could be described by the following equation over the total range of concentrations studied (0.025 - 0.5 M).

$$\eta_0 / \eta = e^{\alpha C}$$

It is interesting to note that this equation was derived by Perrin on the assumptions of a well defined quenching sphere around the donor molecule. Any acceptor outside this sphere was assumed to have no affect on the donor; an acceptor within the sphere was assumed to immediately quench the donor. This physical picture is consistant with an exchange resonance interaction since the probability of energy transfer falls off very quickly as the separation between the molecules increases.

Conclusion. The existence of a physical process called triplet energy transfer has been established. Its properties have been reviewed and found to correspond to those expected for an exchange resonance interaction. Although this mechanism of energy transfer is very frequently encountered, other mechanisms have been found by which similar results can be obtained. Therefore, due caution should be exercised in assigning energy transfer mechanisms.

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MECHANISM OF THE CHEMILUMINESCENCE OF LUCIGENIN

Reported by Charles Leir February 22, 1965

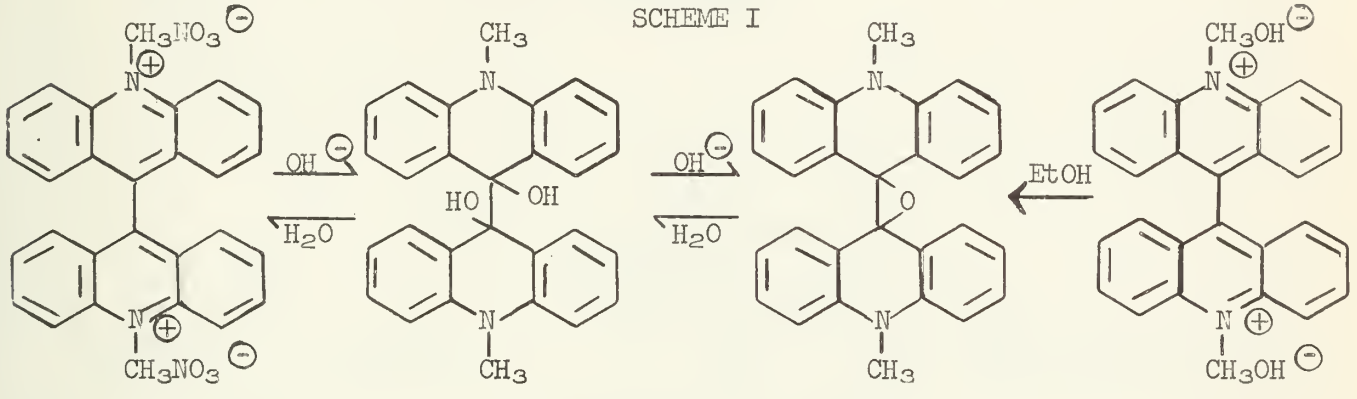
Introduction: A chemiluminescent reaction can be defined as a reaction which has visible or ultraviolet light as one of its products. There are a variety of reactions which exhibit chemiluminescence,[1-12] but the substrates that have been found to be among the most efficient in intensity and duration of light emitted are the 10,10'-dimethyl-9,9'-biacridinium salts.[13]

These compounds have been investigated extensively by many researchers attempting to establish the mechanisms of their chemiluminescent reactions. Reviews of the earlier work are available,[14,15] but this seminar will deal mainly with more recent work concerning biacridinium salts and other closely related compounds.

Lucigenin: 10,10'-Dimethyl-9,9'-biacridinium dinitrate (I), or lucigenin nitrate[13] as it came to be called, is a yellow, crystalline, water soluble solid. Acid or neutral solutions of the compound exhibit intense green fluorescence and are stable indefinitely. Alkaline solutions fluoresce only slightly (ca. 8% of the intensity of acid solutions) and are unstable, forming turbid solutions and brown precipitates in one or two hours.[16] The precipitates were found to be composed mainly of 10, 10'-dimethyl-9,9'-biacridene oxide (II).[17] It is possible that the precipitate was a diol (III) which dehydrated during work-up to give the observed oxide. Indeed, a good method of preparation of II is to pour an aqueous solution of lucigenin hydroxide (IV) into alcohol; II precipitates out immediately in excellent yield.[17]

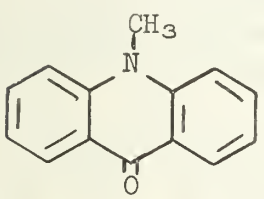
These observations are summarized in scheme I:

SCHEME I



I III II IV

In 1935, Gleu and Petsch discovered that freshly prepared alkaline solutions of lucigenin nitrate, upon addition of dilute hydrogen peroxide, emit a green glow at room temperature. At the completion of the reaction, N-methylacridone (V) was isolated in small yield from a brown precipitate of other unidentified products.[16]

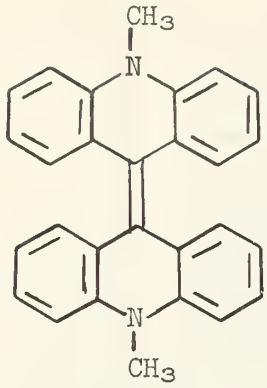


V

Recent work has shown that this brown precipitate was probably composed mainly of 10,10'-dimethyl-Δ9,9'-biacridene (VI) and 10, 10'-dimethyl-9,9'-biacridene oxide (II).[18]

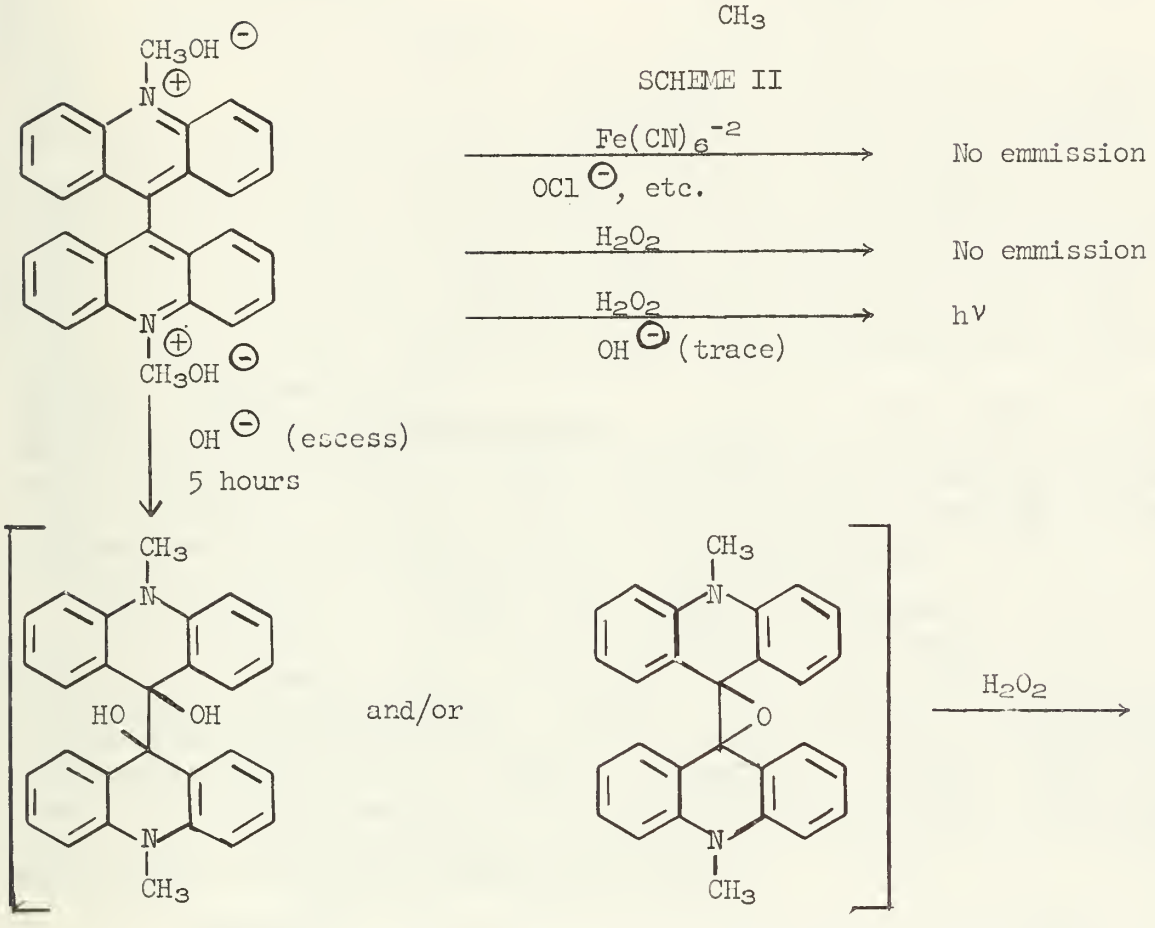
Aqueous alkaline solutions of lucigenin that have stood for five hours and become brown and turbid [extensive formation of diol (III) and/or oxide (II)], nevertheless exhibit almost normal chemiluminescence upon addition of H_2O_2. Solutions of lucigenin hydroxide (IV), prepared by the action of silver oxide on aqueous solutions of lucigenin bromide, do not emit light when H_2O_2 is added until a trace of additional base is added.[17] These observations are strong evidence that the diol (or oxide) does not react directly with H_2O_2, but that some other intermediate reactive species must be formed in the presence of excess base in order for the chemiluminescence reaction to proceed. The reaction has a definite dependence on the presence of hydrogen peroxide. If other oxidizing agents such as $Fe(CN)_6^{-2}$, ClO^-, BrO^-, or MnO_4^- are used, no chemiluminescence is observed.[16]

These findings are summarized in scheme II.

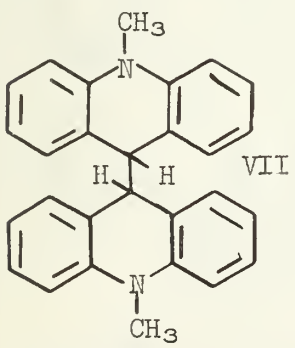


VI

SCHEME II

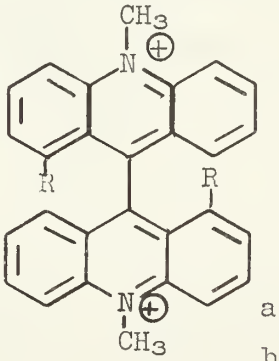


The 9,9' positions were further established as the primary centers of reactivity by Grigorovsky and Simeonov who found that aqueous hydrogen peroxide - pyridine solutions of dimethylbiacridene (VI), and also dimethylbiacridene oxide (II) gave chemiluminescence which appeared identical to that of lucigenin.



VII

However, dimethylbiacridan (VII) did not **chemiluminesce** under the same conditions even with added base.[17] Furthermore, lucigenin with substituents on the 1,1' positions (VIII) gives no light emission while substituents at any other position affect only the color of the luminescence, as can be seen in Table 1.



VIII

a. R = CH_3

b. R = OCH_3

Table 1

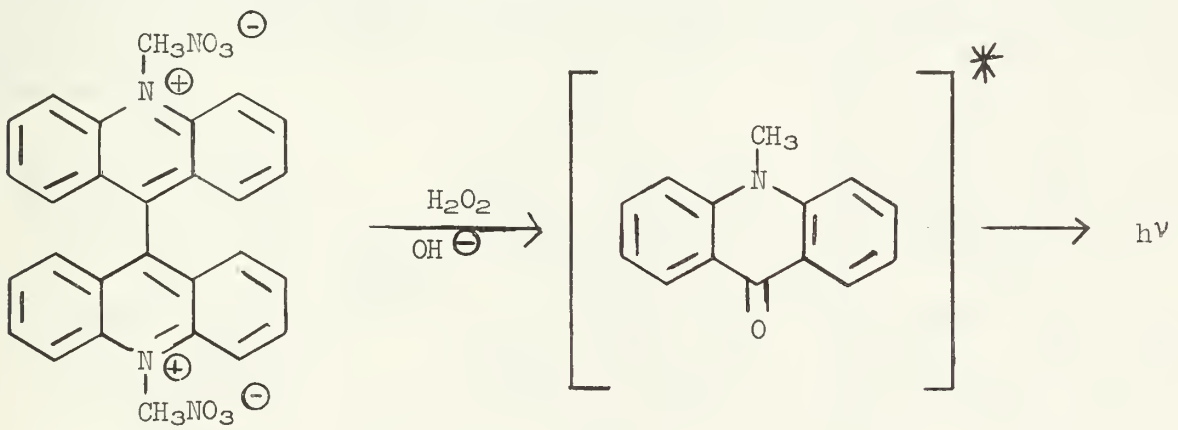
SUBSTITUENTS	CHEMILUMINESCENCE COLOR
10,10'-diethyl	intense green[19]
10,10'-diphenyl	intense green[19]
2,2'-dimethoxy, 10,10'-dimethyl	weak yellow[20]
3,3'-dimethoxy, 10,10'-dimethyl	blue green[20]
4,4'-dimethoxy, 10,10'-dimethyl	orange[20]
2,2', 10,10'-tetramethyl	yellow green[20]
3,3', 10,10'-tetramethyl	intense blue green[20]
4,4', 10,10'-tetramethyl	intense yellow green[20]
1,1', 10,10'-tetramethyl	very weak green - none[20]
1,1'-dimethoxy,10,10'-dimethyl	none[20]

Examination of models shows that with methyl or especially with methoxyl on the 1,1' positions, the 9,9' positions are sterically heavily shielded from attacking species.

Early investigators of lucigenin proposed a variety of mechanisms to account for observations concerning the chemiluminescence of lucigenin.[16,17,22,23,24,26] However, most of their interpretations of these observations were in error, mainly due to lack of knowledge of base-catalysed peroxide reaction mechanisms, and to the lack of spectroscopic measurements sufficiently accurate to allow reliable assignments of the activated species responsible for the luminescence to be made. Only in recent years has real progress been made in the determination of the mechanism of lucigenin chemiluminescence.

Spectra of Lucigenin Chemiluminescence: As early as 1943, Kautsky and Kaiser observed that in very dilute solutions of lucigenin, the color of chemiluminescence was no longer green but blue. The spectrum of the light emitted from the dilute reaction mixture was fairly similar to the fluorescence spectrum of N-methylacridone (V) measured under the same conditions. They proposed that N-methylacridone was the substance principally responsible for light emission.[23]

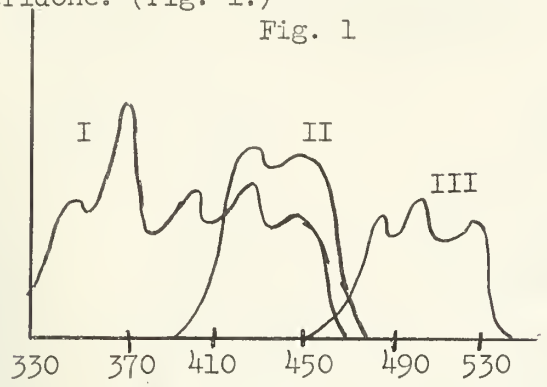
Very recently, J. R. Totter has verified this proposal. He studied a pyridine-alcohol-water mixture (1:1:2) containing KOH (5×10^{-3} molar), H_2O_2 (20×10^{-3} molar); and lucigenin (2.8×10^{-5} molar). Under these ideally dilute conditions, the resulting chemiluminescence spectrum was found to be superimposable with the fluorescence spectrum of N-methylacridone measured under the same conditions.[18] In this mixed solvent system at least, it appears that lucigenin reacts with H_2O_2 and base to form N-methylacridone in an excited electronic state. Once formed, many of these excited molecules emit this excess energy as radiation in returning to the ground state, resulting in chemiluminescence.



Numerous other investigators have published spectra of the chemiluminescence of lucigenin as well as chemiluminescence spectra of possible intermediates and products of the reaction.[21,23-28] None of these reported spectra have been particularly enlightening[18] owing to the use of too great concentrations (10^{-1} - 10^{-4} molar).

The dependence of these spectra on concentration becomes clear when the absorbtion spectrum of lucigenin is compared with the fluorescence spectrum of N-methylacridone. (Fig. 1.)[21]

Fig. 1



I: Absorbtion spectrum of lucigenin
II: Fluorescence spectrum of methylacridone
III: Fluorescence spectrum of lucigenin (in acid)

Since lucigenin absorbs strongly in the region of N-methylacridone emission, much of the blue light emitted by excited acridone molecules will be absorbed by unreacted lucigenin, if it is present in substantial amounts. Lucigenin thus excited could subsequently emit green fluorescence.

However, this is not what is observed as chemiluminescence since lucigenin does not fluoresce appreciably in alkaline solution.[12] Only about 3% of the observed chemiluminescence has been attributed to the fluorescence of lucigenin.[21]

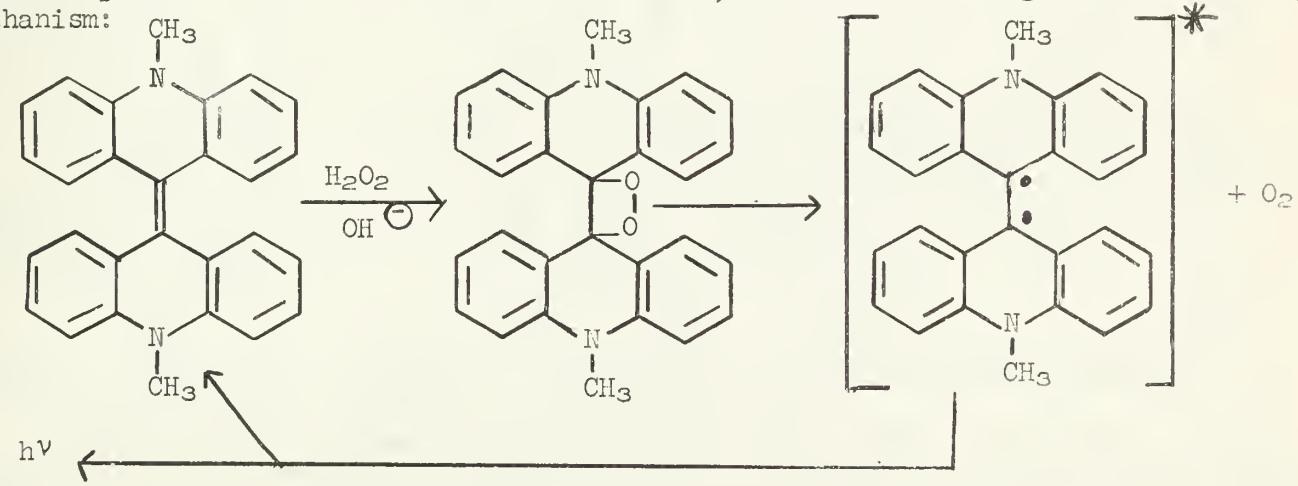
The observed green color of emission in the more concentrated solutions of lucigenin has been attributed mainly to the fluorescence of dimethylbiacridene (VI) and its oxide (II). The compounds are the result of side reactions or could represent an accumulation of intermediates. They are always found at the end of a reaction run in pyridine-water solutions where an excess of lucigenin is used.[18] The fluorescence spectrum of dimethylbiacridene has λ max at 515 mμ, and that of the oxide has λ max at 505 mμ, both well into the green region of the spectrum.[24]

This necessity for using extremely dilute solutions in order to obtain a chemiluminescence spectrum free of extraneous fluorescence is dramatically illustrated by some work of Kariakin[24] involving dimethylbiacridene (VI) and its oxide (II). As shown in Table II, the author compared the chemiluminescence spectra of these compounds with their fluorescence and phosphorescence spectra.

TABLE II

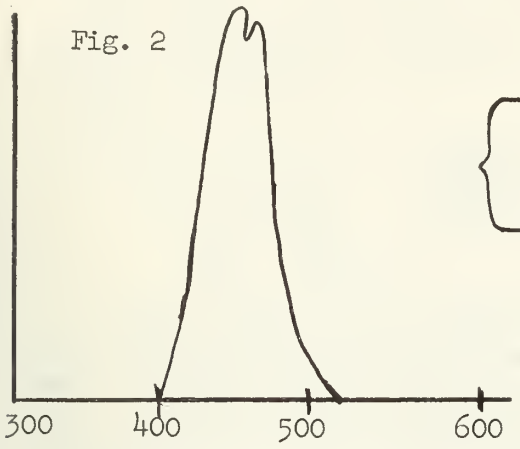
**	Principle maxima of emission (mμ)		
Dimethylbiacridene oxide	550	505	548 (28)
Dimethylbiacridene	525	515	523 (28)
	Chemilum	Fluorescence	Phosphorescence

Since the chemiluminescence and phosphorescence spectra were similar but very different from the fluorescence spectra, Kariakin concluded that a metastable triplet diradical was responsible for the light emission in the chemiluminescence of these compounds. In the case of the biacridene, it arose according to the following mechanism:



The chemiluminescence spectra were obtained in pyridine-water mixtures with substrate concentrations of .2% - 1% (10^{-2}-10^{-1} molar).

J. R. Totter reinvestigated the chemiluminescence of dimethylbiacridene and its oxide (II) in both 50% aqueous pyridine and 50% aqueous alcohol at concentrations of ca. 10^{-5} molar. As can be seen from Fig. 2, the chemiluminescence spectra of these compounds are identical to the chemiluminescence spectrum of lucigenin. Thus, they all yield the same end product - activated N-methylacridone.[18]



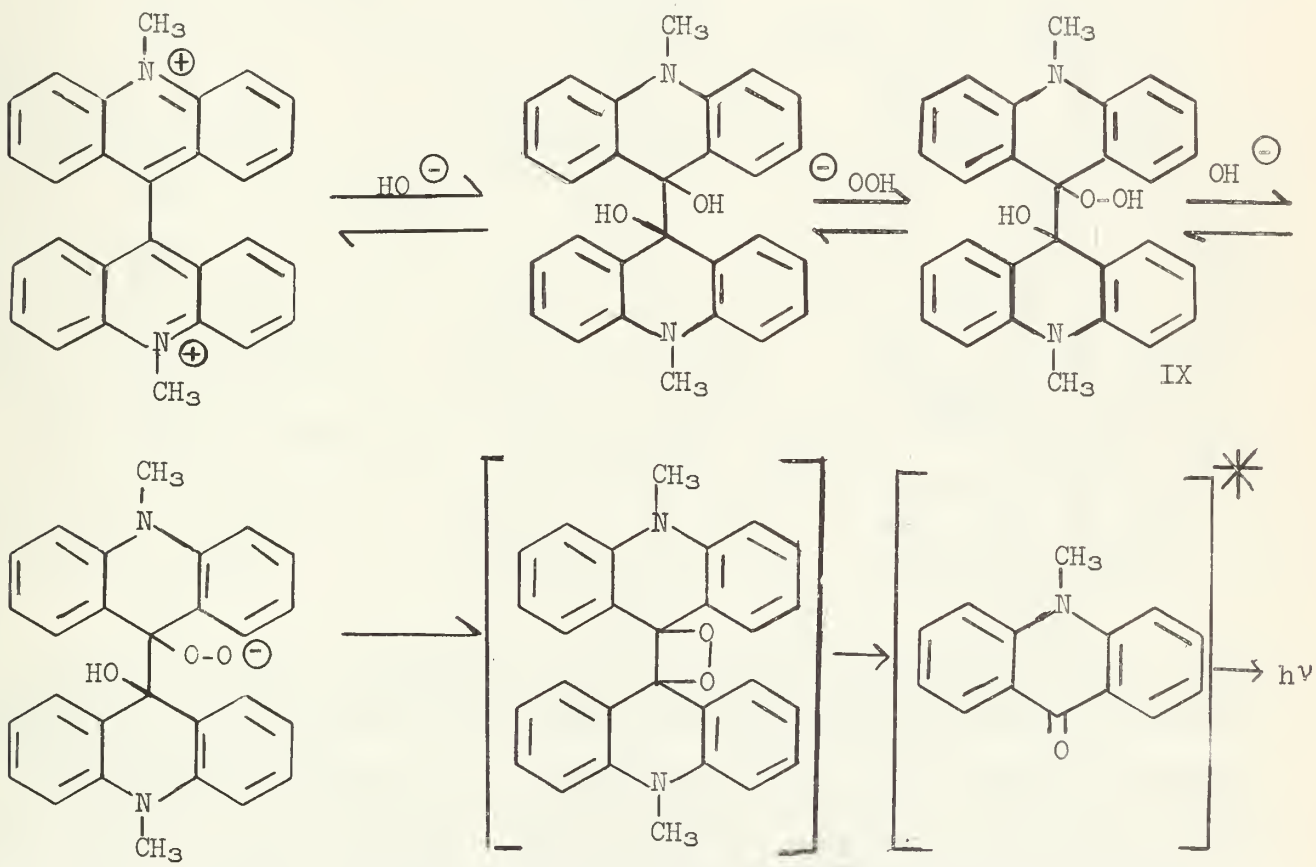
Chemiluminescence spectra of dimethylbiacridene (VI), dimethylbiacridene oxide (II), and lucigenin (I); and fluorescence spectrum of N-methylacridone (V) in 50% aqueous pyridine.

At the high concentrations of substrates he was using, Kariakin was not observing the true chemiluminescence but rather the phosphorescence of his starting material. The acridone, formed in an excited state, transfers its energy to the starting material which subsequently emits the light mistaken for chemiluminescence.

Since these two lucigenin derivatives give rise to the same major end product as lucigenin itself, there is some question as to whether they are intermediates in lucigenin chemiluminescence or merely by products that can still react to form activated N-methylacridone.[18] This has not yet been determined.

McCapra and Richardson have recently proposed the following mechanism for the chemical reaction of lucigenin which leads to activated N-methylacridone.[29]

SCHEME III



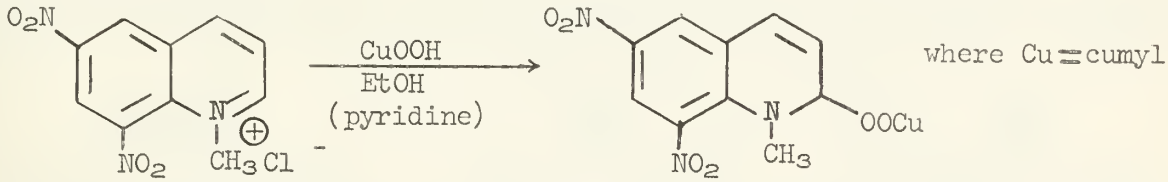
Formation of the diol or even of a mono alcohol is not a necessary step and it is doubtful if the first reaction is readily reversible.

Support for this scheme is found in the fact that ^{-}OOH, a weaker base than hydroxide, is a much stronger nucleophile. It is 35 times more reactive toward benzyl bromide than is hydroxide ion (S_N2 mechanism) and is 200 times more reactive toward

the carbonyl group in ester hydrolysis.[30]

This mechanism can explain the early observation of the inertness of lucigenin hydroxide (IV) toward hydrogen peroxide. Until there is a slight amount of free base available to react with the incipient hydroperoxide (IX) and form the peroxyanion, the chemiluminescence reaction is not observed. (See page 25 and Scheme II).

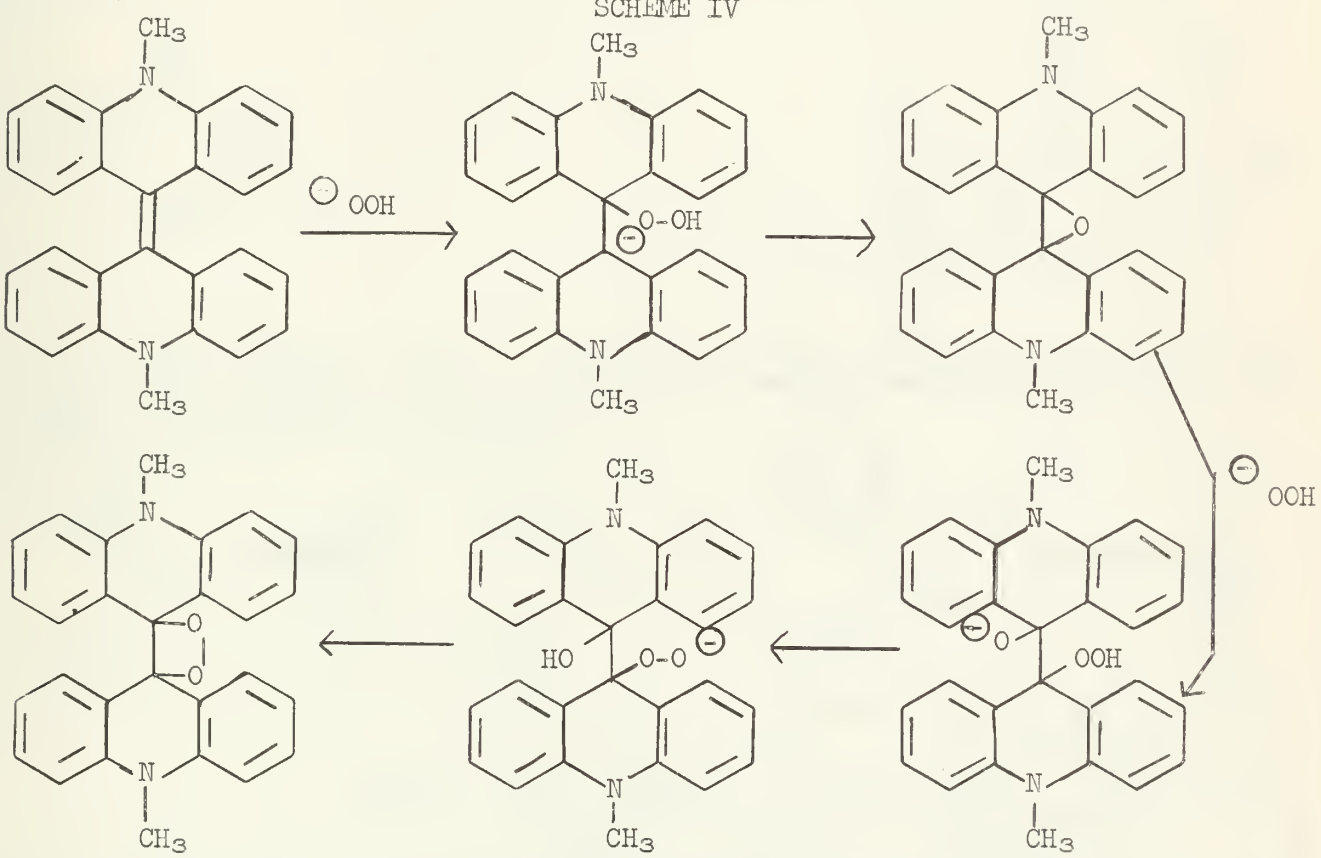
The ability of nitrogen heterocycles of the acridinium type to accept the strongly nucleophilic peroxyanion has been further demonstrated recently by the following reaction.[31]



where Cu = cumyl

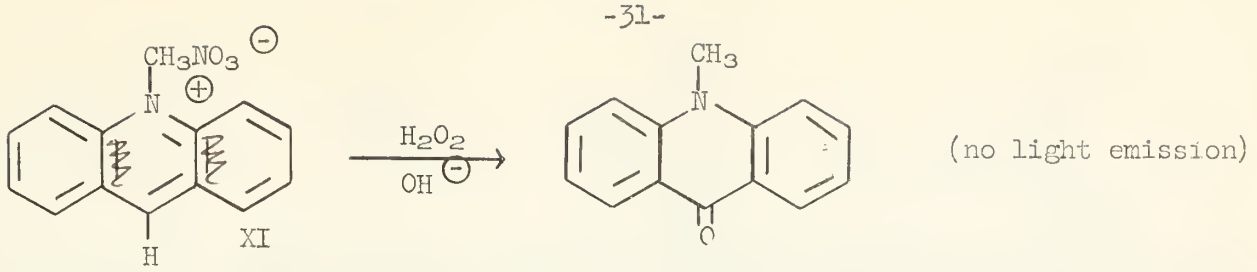
No one has, as yet, suggested any mechanisms by which dimethylbiacridene (VI) and its oxide(II)exhibit chemiluminescence, but since they both give rise to the same activated end product (N-methylacridone), it is probable that they both form this product's immediate precursor, the four membered peroxide ring. One conceivable manner in which this intermediate might arise from both compounds is illustrated in Scheme IV.

SCHEME IV



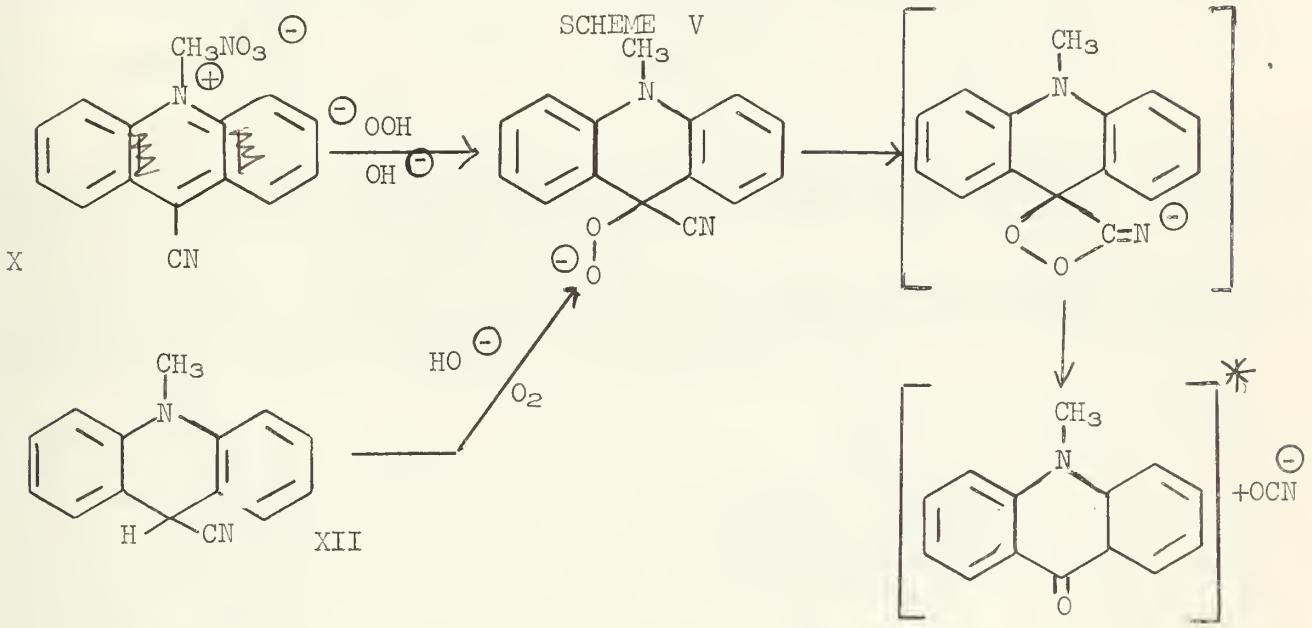
However, it must be emphasised that this scheme is highly speculative, and establishment of the mechanism will require further experimentation with these lucigenin derivatives.

Assuming the validity of the lucigenin chemiluminescence mechanism, McCapra and Richardson anticipated that 9-cyano-10-methyl acridinium nitrate (X) should also exhibit chemiluminescence. Indeed, when this compound was treated with ethanolic alkaline hydrogen peroxide, a blue glow was emitted which was identical in every respect to the fluorescence spectrum of N-methylacridone (λ max 442 mμ) measured under the same conditions. Moreover, the acridone was isolated from the reaction mixture in almost quantitative yield. Under the same conditions, unsubstituted N-methyl-acridinium nitrate (XI) gives quantitative yields of the acridone but no emission of light.

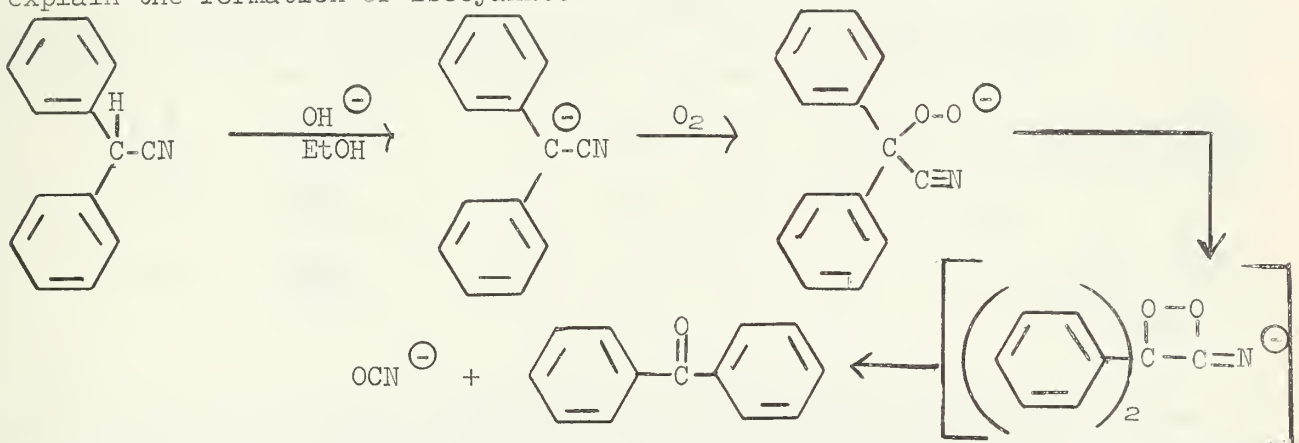


Alkali solutions of 10-methyl-9-cyanoacridan (XII), however, give the same luminescence and yield of end product as the acridinium nitrate when molecular O_2 is bubbled through the solution. The following mechanisms were proposed.[29]

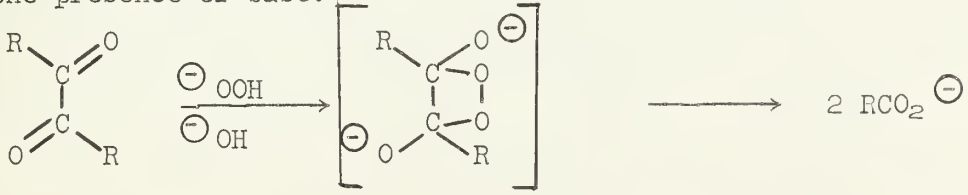
SCHEME V

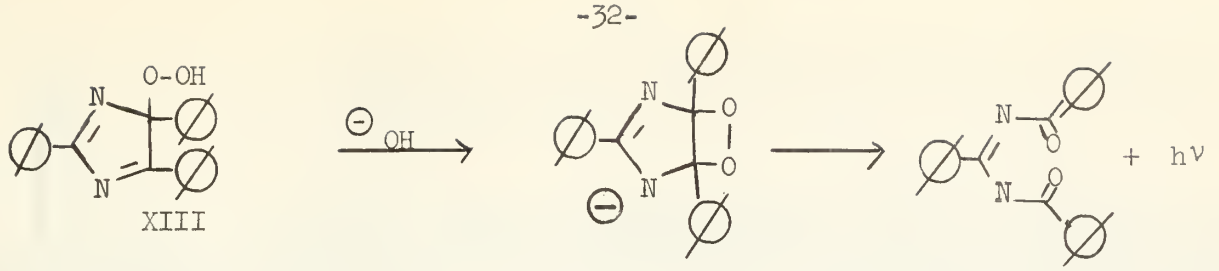


The latter reaction of the acridan (XII) is almost completely analogous to the autoxidation of secondary nitriles where a four membered peroxide ring is also used to explain the formation of isocyanate.[32]



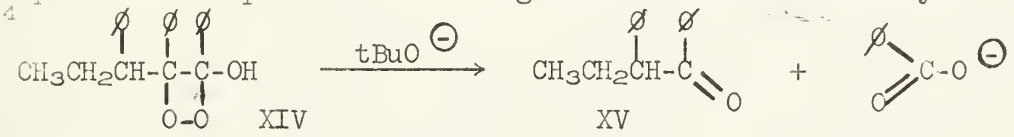
Four membered peroxide ring intermediates have been shown to be involved in the oxidation of α,β diketones by hydrogen peroxide and base,[33] and have been very recently suggested as intermediates in the chemiluminescence of lophine hydroperoxides (XIII) in the presence of base.[5]





XIII

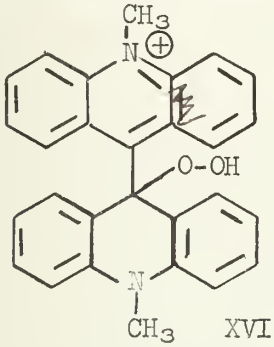
W. von E. Doering employed 4-membered peroxide ring intermediates to explain the base catalysed autoxidations of various aromatic ketones. He claims to have isolated such an intermediate, 1,2,3-triphenyl pentene-1-ol peroxide (XIV), and that this compound in the presence of base gave benzoic acid and ethyldesoxybenzoin (XV).[34]



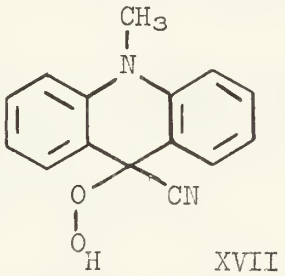
XIV XV

The 1,2 dioxetane has been a postulated intermediate of every mechanism ever proposed to explain lucigenin chemiluminescence but it has never been isolated. It is possible that the species represented by the four membered ring is actually a transition state and not a true intermediate.[29]

Unfortunately, no one has yet synthesized lucigenin hydroperoxide (XVI) or 9-cyano-9-hydroperoxy-10-methylacridan (XVII) and demonstrated that these compounds yield N-methylacridone and light in the presence of base.

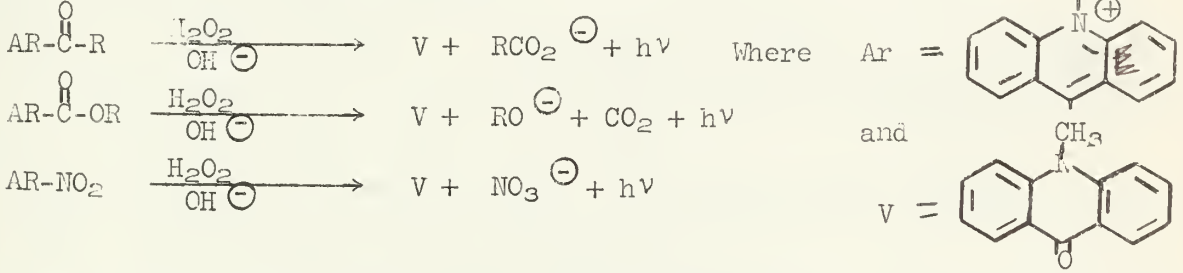


XVI



XVII

Since 9-cyano-N-methyl acridines give chemiluminescence, one might expect other analogously substituted N-methylacridines to give similar results. The following few examples give the products expected if the mechanism were general:



Where Ar =

and V =

The reactions of the corresponding N-methyl-9-substituted acridans (XII) with molecular O_2 in the presence of strong base should also give rise to the same products.

The majority of evidence seems to support a McCapra and Richardson type mechanism for lucigenin chemiluminescence, at least in non-aqueous or mixed aqueous - organic solvents, using hydrogen peroxide and base at room temperature. Nevertheless, there still remain a number of isolated observations for which the mechanism does not seem to offer reasonable explanations. For instance, it has been shown that in mixed aqueous-organic solvents, chemiluminescence is the result of N-methylacridone fluorescence.[18] However, as Fig. 3[18] will show, the nature of the emitting molecule in fully aqueous solution is still a matter for speculation.

Totter suggests that the N-methylacridone fluorescence and lucigenin chemiluminescence spectra are significantly different in fully aqueous solutions, possibly because a short-lived hydrate of the acridone is responsible for emission. N-methylacridone is still the only fluorescent end product seen immediately following chemiluminescence.[18]

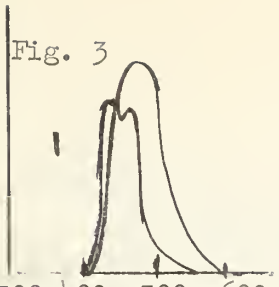


Fig. 3 I. Fluorescence spectrum of N-methylacridone and chemiluminescence of 10^{-5} molar lucigenin in pyridine-alcohol-water (1:1:2).
II. Chemiluminescence of ca. 10^{-5} molar lucigenin in pH 10.4 water.

However, at least two other possibilities exist: 1) An entirely different mechanism might be operative in fully aqueous solutions. 2) The chemiluminescence spectrum of aqueous lucigenin might yet be superimposable with the fluorescence spectrum of N-methylacridone in water. No one has yet reported the fluorescence spectrum of the acridone in water, presumably due to its insolubility; but the required change in spectrum is not inconceivable.

Other observations which appear to be incompatible with the McCapra and Richardson nucleophilic mechanism are: 1) Alkaline solutions of lucigenin exhibit intense, brief emission in the presence of molecular oxygen and various reducing agents (hydrosulfide, sulfide, vanadite, stannite, etc.).[16] 2) Alkaline solutions of lucigenin upon heating in the presence of molecular oxygen give strong light emission. This luminescence is retarded by hydroquinone and sodium sulfite.[22] 3) If alcohol solutions of dimethylbiacridene (VI) and dimethylbiacridene oxide (II) are shaken in air, spontaneous chemiluminescence is observed.[18]

These results suggest that, under these conditions, free radicals might possibly be involved in the mechanism. No one, as yet, has attempted to verify or disprove this possibility.

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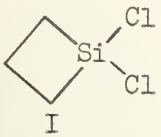
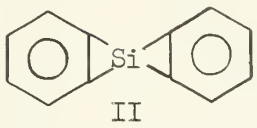
CYCLIC ORGANOSILICON COMPOUNDS

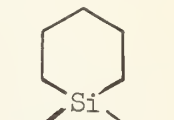
Reported by J. David Angerer March 15, 1965

The first report of cyclic organosilicon compounds in the chemical literature appeared in 1887, when Hart claimed to have prepared cyclotrimethylenedichlorosilane (I) and "o-diphenylenesilane" (II).[1] Widdowson, who carefully repeated Hart's work, was unable to isolate any traces of I or II.[2] He therefore concluded that Hart's compounds were mixtures and should be stricken from the literature. The first authentic cyclosilicon compound was 1,1-dichloro-1-silacyclohexane, III, prepared by Bygden in 1915.[3]


I

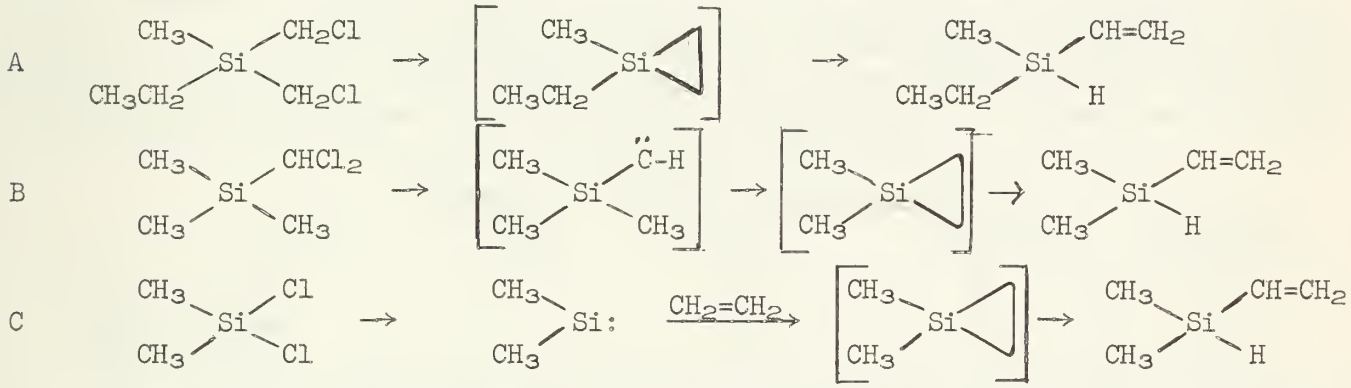

II

In recent years, ever increasing attention has been paid to the synthesis of cyclic organosilicon compounds to the end that their chemical properities might be studied and compared to those of their carbocyclic analogs. Reviews have appeared[4,5,6,7,8] concerning organosilicon chemistry in general, but only one review[9] has appeared concerning cyclic organosilicon compounds. It will, then, be the object of this seminar to review the preparation and reactivities of these compounds.


III

Three-membered rings. As of this time, no successful synthesis of a three-membered ring compound with silicon in the ring has been reported and substantiated. A compound termed a "silirene" was reported by Vol'pin and co-workers, but the actual structure of this product has been attacked by other workers. This will be treated later in the seminar.

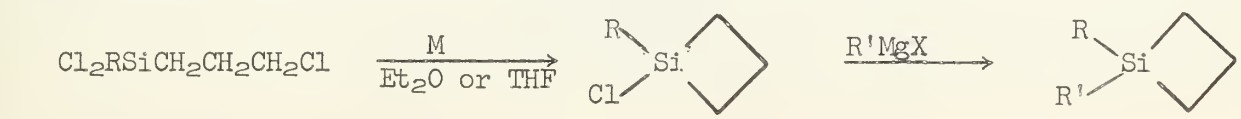
Skell and coworkers[10] have presented evidence that a silacyclopropane was synthesized but that its thermal instability prevented its isolation. They conducted reactions A-C, isolating the products indicated.



All reactions were carried out in an alkali-metal vapor atmosphere at temperatures of 260° - 280°. Although times of residence in the reaction zone of ~1 second were used, no silacyclopropane was observed. However, the authors feel the products isolated can best be explained by such an intermediate. Cyclopropanes are formed by analogous reactions in good yields. The authors explain the large difference in thermal stability between cyclopropanes and silacyclopropanes by added strain in the latter due to the size of the silicon atom, making the C-Si-C bond angle ~48°.

Preparation of four- and higher-membered rings. A wide variety of cyclic organosilicon compounds has been prepared. In fact, the difficult step of the synthesis is not the ring closure step, as might be suspected, but the introduction of functional group onto the ring once it is formed. This cannot be done beforehand, since ring closure is effected by magnesium or the alkali metals.

Silacyclobutanes have been prepared by Vdovin and co-workers[11] by the following procedure:



M = Na, Li, Mg

Table I shows the types of compounds prepared.

Table I

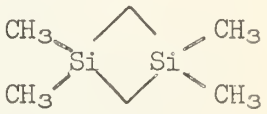
R	R'	Yield (%)
CH_3	CH_3	74
CH_3	C_2H_5	68
CH_3	n-C_4H_9	56
CH_3	ϕ	53
CH_3	ϕ-CH_2	87
CH_3	CH_2=CH-CH_2	60

Kriner[12] and Knoth and Lindsey[13] have prepared four-membered rings which contain 2 silicon atoms. The former accomplishes the synthesis in one step:

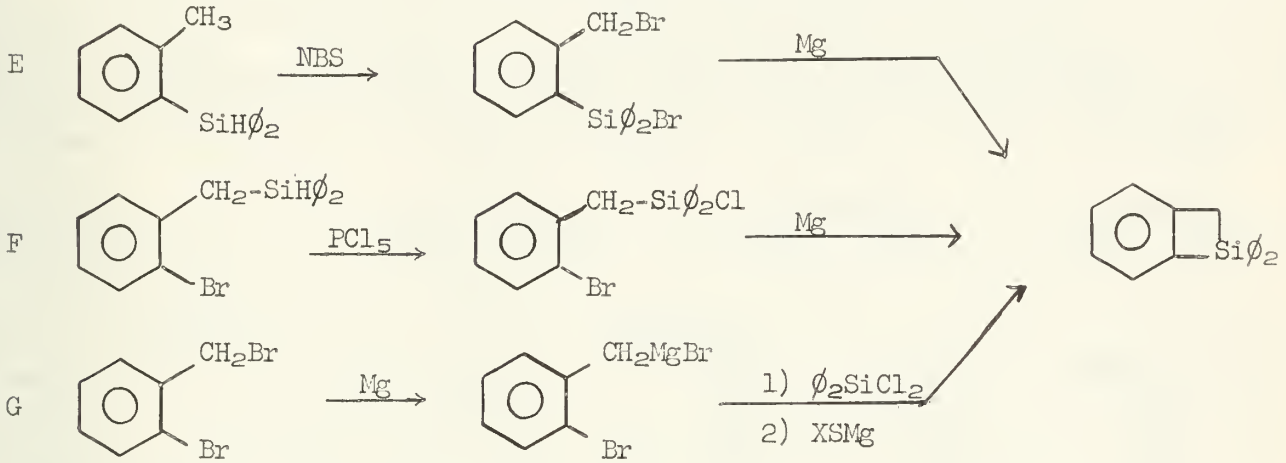
$$n ClCH_2Si(CH_3)_2Cl + nMg \longrightarrow [(CH_3)_2SiCH_2]_n + nMgCl_2$$

where n = 2,3, while the latter require many steps, the ring-closing reaction being:

$$FSi(CH_3)_2\text{-}CH_2\text{-}Si(CH_3)_2\text{-}CH_2Cl \xrightarrow{Mg}$$



Gilman[14] has prepared the 2:3 benzo-1-silacyclobutene series by three routes:

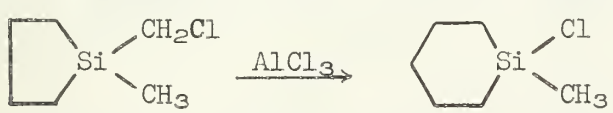


Syntheses of higher-membered rings have been accomplished by analogous reactions.[15,16,17,18] West[18] noted two trends in the synthesis: (1) The yield is highest for a six-membered ring, somewhat lower for a five-membered ring and very much lower in the case of a seven-membered ring. This trend follows that of ring closure in the carbocyclic system. (2) The yield of cyclic product increases as the number of chlorine atoms on the silicon increases (see Table II).

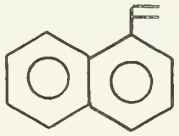
Table II - % Yields of Cyclic Silanes

Grignard Reagent	with	$SiCl_4$	CH_3SiCl_3	CH_3SiHCl_2
$BrMg(CH_2)_4MgBr$		51	47	40
$BrMg(CH_2)_5MgBr$		69	62	47
$BrMg(CH_2)_6MgBr$		11	--	4

A novel ring-expansion reaction was reported by Vdovin,[19] when he noticed that 1-methyl-1-chloromethyl-1-silacyclopentane rearranged to 1-methyl-1-chloro-1-silacyclohexane at room temperature under the influence of catalytic amounts of aluminum chloride in yields of 80% or more. No mechanism was proposed to explain the change.

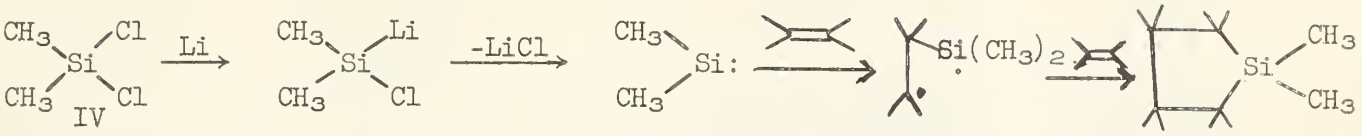


Nefedov and co-workers[20] have reported an interesting reaction leading to the formation of a silacyclopentane. They found that dichlorodimethylsilane (IV), when treated with lithium metal in tetrahydrofuran and in the presence of styrene, produced a diphenyl-1,1-dimethyl-1-silacyclopentane in 30% yield. They obtained analogous products with 1-vinylnaphthalene (VI) and with methyl methacrylate.



VI

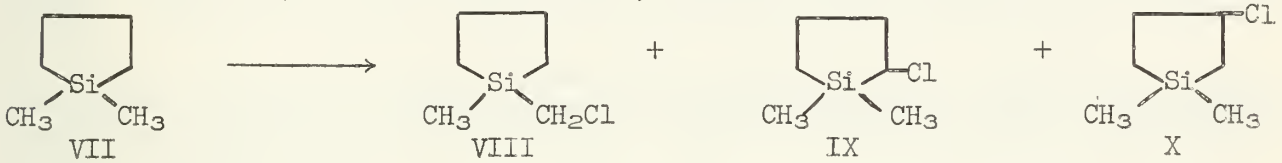
They propose the following mechanism to account for the change:



Unfortunately, the products were not fully characterized.

The route to silacyclopentadiene -2,4. In 1959, Mironov and Nepomnia[21] introduced a method that has proven useful for the introduction of functional groups on the alkyl part of an alkylsilane - chlorination with sulfuryl chloride and benzoyl peroxide. They prepared the 3-chloro derivative of 1,1-dichloro silacyclopentane, which yielded 1,1-dichloro-1-silacyclopentene-2 upon pyrolysis with quinoline.

Fessenden[22] found that the predominance of chlorination by chlorine or sulfuryl chloride gave chlorination on the 1-methyl groups when 1,1-dimethyl-1-silacyclopentane (VII) was used. Use of free radical catalysts was found to accelerate the reaction and to change the distribution between the 2- and 3-isomers (See Table III). Without the catalyst, more IX was produced, whereas when the catalyst was present more

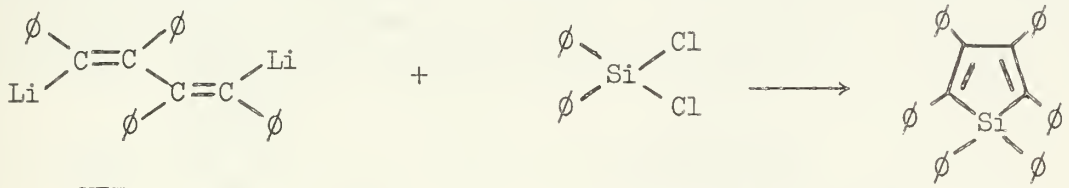


X was isolated.

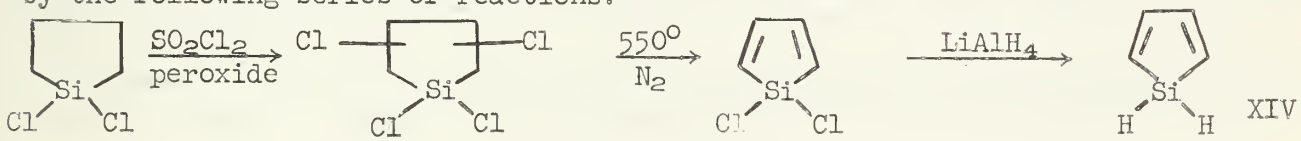
Table III

Reagent	%VIII	%IX	%X	%monochloro
Cl_2	63	20	17	52
Cl_2-hν	52	18	30	55
SO_2Cl_2	74	23	2	13
SO_2Cl_2-Bz_2O_2	62	11	27	39

The first silacyclopentadiene to be prepared was hexaphenylsilacyclopentadiene, (XIII),[23] synthesized from diphenyldichlorosilane (XI) and 1,4-dilithio-1,2,3,4-tetraphenylbutadiene (XII).

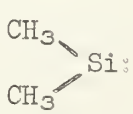


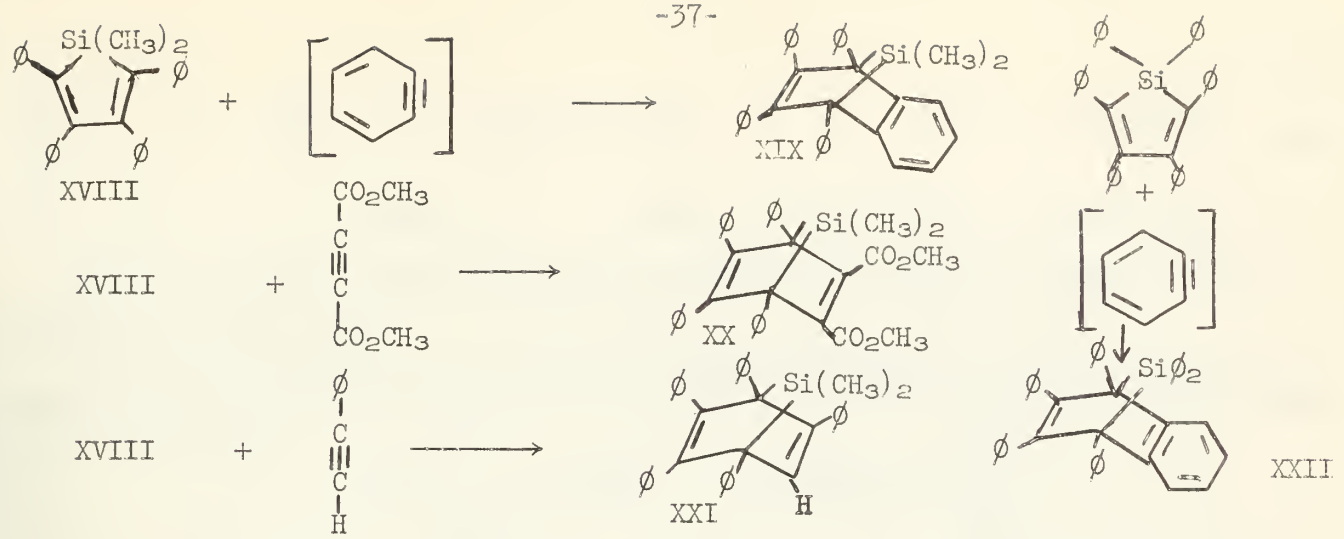
Benkeser and co-workers[24,25] reported the synthesis of the parent compound (XIV) by the following series of reactions.



However, a retraction has appeared.[55] Two obvious reasons for preparing compounds such as XIV are: (1) the possibility of a pseudo-aromatic system such as XV, analogous to cyclopentadiene, and (2), a possible entry into the 7-silanorbornadiene system(XVI). The former problem will be dealt with later in the seminar.

Gilman and co-workers[26,27] were successful in preparing the 7-silanorbornadiene system, and with it a possible dimethylsilylene (XVII) precursor. This was accomplished by means of Diels-Alder reactions. Some of the compounds prepared are illustrated below.

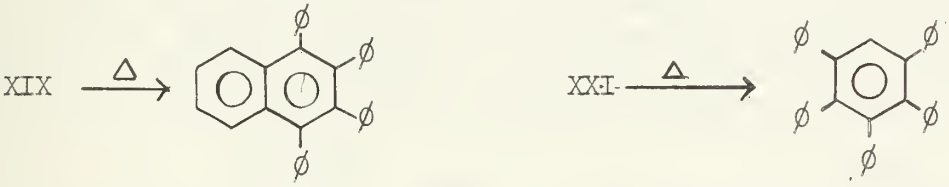




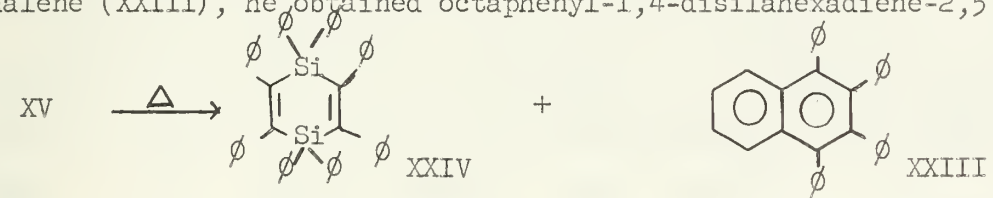
The n.m.r. spectrum of 2:3 benzo-7,7-dimethyl-1,4,5,6-tetraphenyl-7-silanorbornadiene (XIX) showed the presence of two different methyl groups with bands at δ=0.71 p.p.m. and δ=-0.02 p.p.m. The aromatic/aliphatic proton ratio was 4.0 (calculated 4.0).

The n.m.r. spectrum of XX contained a sharp singlet at δ=3.63 p.p.m. (area 6) assigned to $O\underline{CH_3}$. The methyl groups on silicon appeared as a pair of singlets centered at δ=0.54(area 3) and δ=0.44 p.p.m. (area 3). The aromatic/aliphatic ratio was 1.60 (calculated 1.67).

Decomposition of the 7-silanorbornadiene derivatives by thermal processes gave

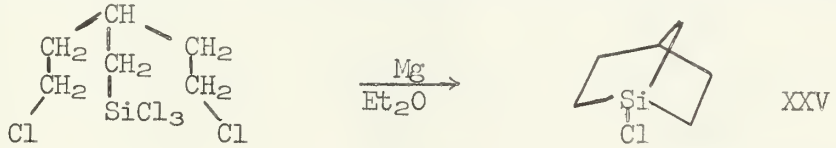


benzene derivatives and a polymeric substance. The polymeric substance was shown to be $[(CH_3)_2Si]_n$ which suggested to Gilman that dimethylsilylene may have been produced. For this reason, he pyrolyzed 2:3 benzo-1,4,5,6,7,7-hexaphenyl-7-silanorbornadiene (XXII) in the presence of diphenylacetylene. In addition to 1,2,3,4-tetraphenylnaphthalene (XXIII), he obtained octaphenyl-1,4-disilahexadiene-2,5 (XXIV) in approximately



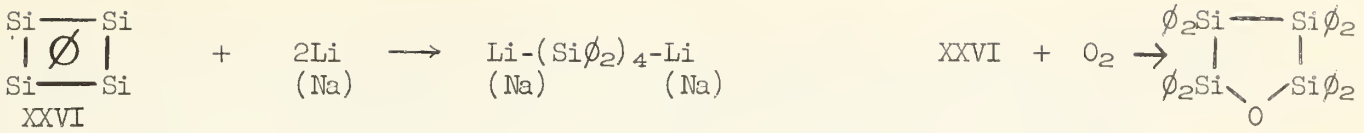
63% yield. The polymer $(ø_2Si)_n$ was recovered unchanged from a thermolysis in the presence of diphenylacetylene. This indicates that there may be a species ($Siø_2$) present during the reaction.

Sommer[28] has synthesized 1-chloro-1-silabicyclo[2.2.1]heptane (XXV) by the following procedure in order to study displacement reactions on bridgehead silicon:



This will be discussed in the next section in relation to the reactivities of various ring systems.

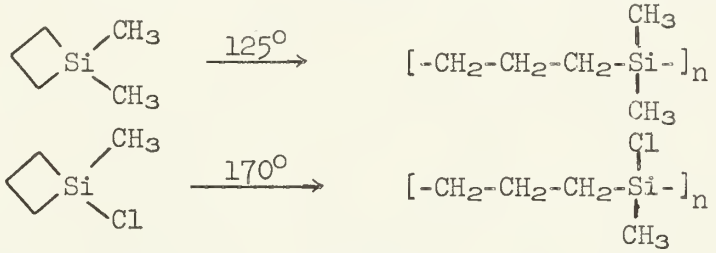
Reactivities in the cyclosilane series. It has been stated earlier that silacyclopropanes appear to be extremely unstable, more so than cyclopropane. It has been observed that silacyclobutanes are extremely reactive. The latter react readily with lithium and sodium metals,[30,34] iodine,[31,32] bromine,[31] certain halogenated solvents such as sym-tetrachloroethane,[31] oxygen[31] and phenyllithium.[33] These reactions are illustrated below for octaphenyl cyclotetrasilane (XXVI), probably the most widely studied cyclic organosilicon compound.



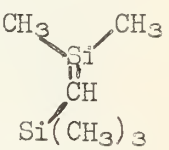
XXVI + I_2 ⟶ I-$(Si\phi_2)_4$-I XXVI + $CHCl_2$-$CHCl_2$ ⟶ Cl-$(Si\phi_2)_4$-Cl

The five-membered ring homolog, decaphenylcyclopentasilane, reacts with ring opening with bromine and alkali metals, but is stable to oxidizing agents, iodine and halogenated solvents.[35]

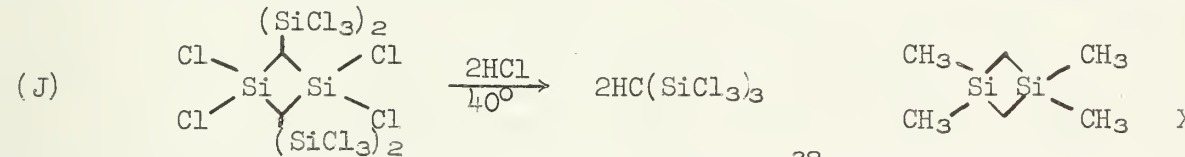
Vdovin and coworkers have found that silacyclobutanes undergo ring opening at temperatures of 125-180°, giving rise to polymers, where five-and six-membered rings are not affected.[36]



The extreme reactivity of silacyclobutanes caused Fritz and Grobe to claim that they had isolated 1-trimethylsilyl-2-methyl-2-silapropene (XXVII), a compound containing a carbon-silicon double bond, from the pyrolysis products of tetramethylsilane.[37] They stated that their compound added hydrogen bromide and bromine. However, a structure proof of XXVII was not attempted. Müller and co-workers[38] stated some misgivings as to the proposed structure XXVII. They cited evidence of ring cleavage of a four-membered ring with hydrogen chloride (J). They proposed that the compound actually has structure XXVIII, which could undergo ring cleavage by bromine and hydrogenbromide.



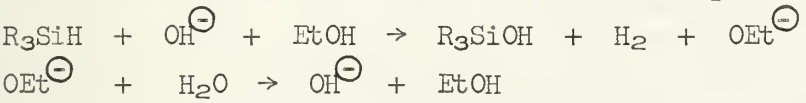
XXVII



XXVIII

This structure was confirmed by Fritz and coworkers[39] and the claim to have prepared a compound with a silicon-carbon double bond was retracted. As of this time, no authenticated carbon-silicon double bond has been prepared.

Sommer and co-workers[40] have studied the kinetics of the reaction of triorganosilanes with hydroxide ion in 95% ethanol. The reaction proceeds according to scheme I.[42] Hydroxide is not consumed and hydrogen is evolved quantitatively. The reactions were observed to have a first-order dependence on the silane and on hydroxide,



Scheme I

and are thus formally similar to S_N2 displacements on carbon. The reactions were carried out on compounds XXIX-XXXIII. Relative rates are tabulated in Table V.

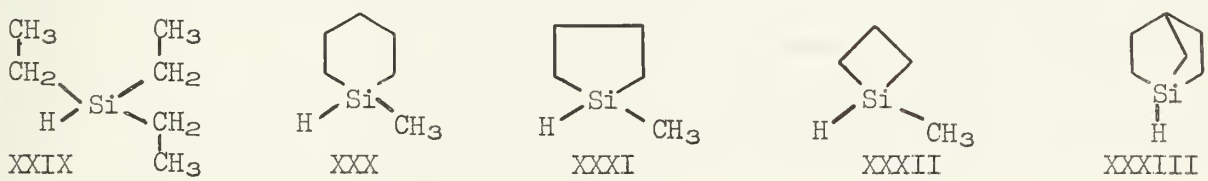


Table V

Compound	rate relative to XXIX
triethylsilane (XXIX)	1
1-methyl-1-silacyclohexane (XXX)	10^{-1}
1-methyl-1-silacyclopentane (XXXI)	10
1-methyl-1-silacyclobutane (XXXII)	10^4-10^5 *
1-silanorbornane (XXXIII)	10^3

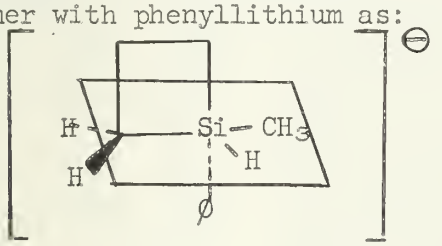
* the four-membered ring compound (XXXII) gives 60% of the theoretical hydrogen at

a very fast rate, and the remaining 40% at a rate that is slower by about three powers of ten. This is due to hydrogen evolution from sym-di-n-propyldimethyldisiloxane, which is formed by ring opening of XXXII (carbon-silicon bond cleavage by hydroxide in competition with the evolution of hydrogen from XXXII).

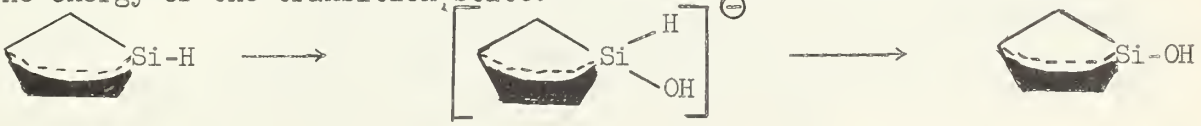
It is seen that hydride displacement by hydroxide proceeds far more rapidly at bridgehead and four-membered ring silicon atoms than at silicon in five and six-membered rings. This is a reversal of the structure-reactivity relationships observed at carbon when the same comparisons are made.[41]

Factors contributing to the reactivity of silacyclobutanes. To explain the difference in reactivities between carbocylic rings and rings containing a silicon atom, West[44] stated that, in spite of the increased size of silicon over carbon, the angular strain in silacyclobutane is probably no greater than in cyclobutanes, since the tetrahedral angle of silicon is reported[45] to be more easily deformed than than that of carbon. He preferred to attribute the more facile ring opening of silacyclobutanes to the availability of mechanisms to the latter which are not available to cyclobutane. Gilman and co-workers[14] concur with West and believe that the mechanisms in point are due to the participation of the d-orbitals on silicon during a substitution reaction, resulting in the formation of a pentacovalent addition complex of the type dsp^3. The enhanced reactivity of four-membered rings containing one silicon atom as compared to their five-membered ring analogs is attributed by Sommer[40] to the angular strain present in the ring. Gilman and co-workers feel that the observed difference in reactivity of the preceding compounds can be explained by a qualitative consideration of both the ground- and transition-state energies of these compounds. In view of the distortion of bond angles resulting in the formation of a considerably strained ring system, the four-membered ring system should possess a more energetic ground state than the five-membered ring. This would favor ring opening of the former in preference to the latter.

Sommer[40] has presented a theoretical consideration of the transition state of a silacyclobutane derivative in nucleophilic substitution reactions. He explains the high reactivity of 1-methyl-1-silacyclobutane in hydrolysis reactions by considering structure-reactivity relations resulting from steric factors. He noted that 1-methyl-1-silacyclobutane opened 10^3-10^4 times as fast as 1-methyl-1-silacyclopentane. He pictures the pentacovalent addition complex of the reaction of the former with phenyllithium as:



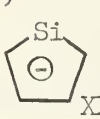
(an analogous situation would hold for attack by hydroxide ion leading to replacement of hydride.) Sommer proposes three considerations: (1) since the ring substituents in the four-membered ring are "pulled back" (relative to the five-membered ring) away from the path of the attacking reagent, the formation of this complex should be facilitated. (2) the C-Si-C bond angle in the transition state as pictured would be expected to be about 90°. Since the ring angle in the four-membered ring should be close to this value, much less internal strain should be introduced during the formation of the complex from the four-membered ring than from the five-membered ring. (3) Owing to increased crowding of the ring substituents in the transition state relative to the ground state of the four-membered ring, an increase in ring strain should result during the formation of the former. The same considerations could be used to explain the reactivity of the silanorborane. The reactivity of the latter would be expected to be decreased, as compared to the four-membered ring, since the angles of the supposed trigonal bipyramid intermediate would be deformed (see below), raising the energy of the transition state.

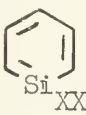


Pseudo-aromatic compounds. One of the most obvious of questions to be raised when dealing with heterocyclic compounds is that of possible aromaticity. Since silicon is in the same column of the periodic table as is carbon, we might suspect the

existence of silicon analogs of the cyclopropenium cation (XXXIV), the cyclopentadienyl anion (XXXV), benzene (XXXVI) and the tropylium ion (XXXVII).


XXXIV

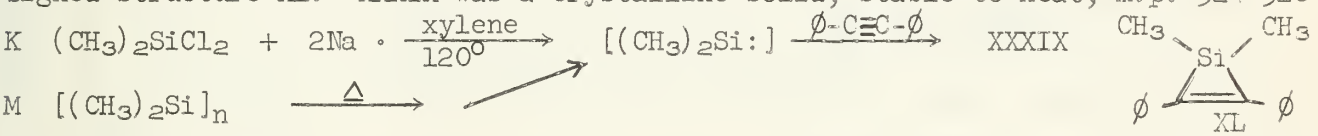

XXXV


XXXVI


XXXVII

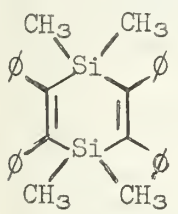

XXXVIII

On the basis of previous parts of this discussion, we must tend to eliminate compounds such as XXXVI, XXXV, XXXVII from our consideration at the present time, since no report of a silicon-carbon double bond has ever been substantiated.[37,38,39] A literature search reveals that no published attempts have been made to prepare compounds such as XXXVII or XXXVI. Since a three-membered silicon heterocycle has never been prepared, forms such as XXXIV are improbable. Vol'pin and co-workers, however, felt that a structure such as XXXVIII would not only be possible, but would also possess added stability because of the possibility for not only p-p-p interaction, but also for p-p-d interaction, utilizing the vacant 3d orbitals of silicon.[49,50] They discount compounds of the type XXXIV, since all attempts to isolate a species R_3Si^+ or to prove its formation in a chemical reaction have been in vain. Using reactions K and M, they isolated a compound XXXIX to which they assigned structure XL. XXXIX was a crystalline solid, stable to heat, m.p. 324-328

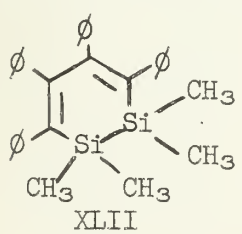


(without decomposition) which could be sublimed at temperatures greater than 200°. It was not oxidized in air, nor did it add bromine in carbon tetrachloride. The infra-red spectrum of XXXIX showed bands at 1248, 795, assigned to the $Si(CH_3)_2$ group,[51] 1600 (conjugated C=C with aromatic), 696, 752, 1020, 1065 and 1175 cm^{-1} (monosubstituted phenyl). Analytical data gave an empirical formula of $C_{16}H_{16}Si$.

Johnson and Gohlke,[52] however, disagreed with the assignment of structure XL to compound XXXIX. They particularly took exception to Vol'pin's germanium analog of XL. They determined the molecular weight by mass spectrometry and found it to be twice the theoretical value of the germanium analog of XXXIX. They proposed a dimeric structure (XLI) for XXXIX. They also noted that Vol'pin had based his aromatic character on inertness to bromine in carbon tetrachloric, alkali, strong acids, and lack of catalytic hydrogen addition, as well as stability toward heat and oxidation. These properties are known to apply to many silicon and germanium compounds that are not hetero-aromatic, with the exception of bromine addition.[53] They found that the compound XXXIX does decolorize bromine in carbon tetrachloride in one hour at room temperature.


XLI

West[54] presented evidence favoring structure XLI by showing that the tetra-p-tolyl analog of XXXIX shows only one sharp n.m.r. peak for the tolyl methyl protons at δ=2.30. This indicates an equivalent magnetic field for the four methyl groups, discrediting structures such as XLII for the dimer. West suggests that the inertness to bromine is due to steric hindrance and perhaps to the delocalization of the olefinic π-electrons participation of the 3d orbitals of silicon in the π-bonding.


XLII

Benkeser and co-workers[46,47] reported the synthesis of several silacyclopentadienes and of the sila-cyclopentadienide anion. However, this work has been retracted[48,55,56] and, as of this time, no silacyclopentadiene has been prepared and substantiated. Thus, no psuedoaromatic cyclosilicon compounds are yet known.

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SHIKIMIC, QUINIC, AND PREPHENIC ACIDS

Reported by James A. Bonham March 18, 1965

In the past decade a great deal of progress has been made in the understanding of aromatic amino acid biosynthesis.[1-6] Although a complete treatment is beyond the scope of this seminar a brief outline is presented in fig. 1 of a biosynthetic pathway operative in the mutants of micro-organisms. It has been demonstrated the (-)-5-dehydroquinic acid (II),[1,2,5] (-)-5-dehydroshikimic acid (III),[1,2,5] (-)-shikimic acid (IV),[1,2] (-)-shikimic acid-3-enolpyruvate-5-phosphate (V),[6] (-)-chorismic acid (VI),[4] and prephenic acid (VII),[2] but not quinic acid (I), are normal intermediates in microbial aromatic biosynthesis.

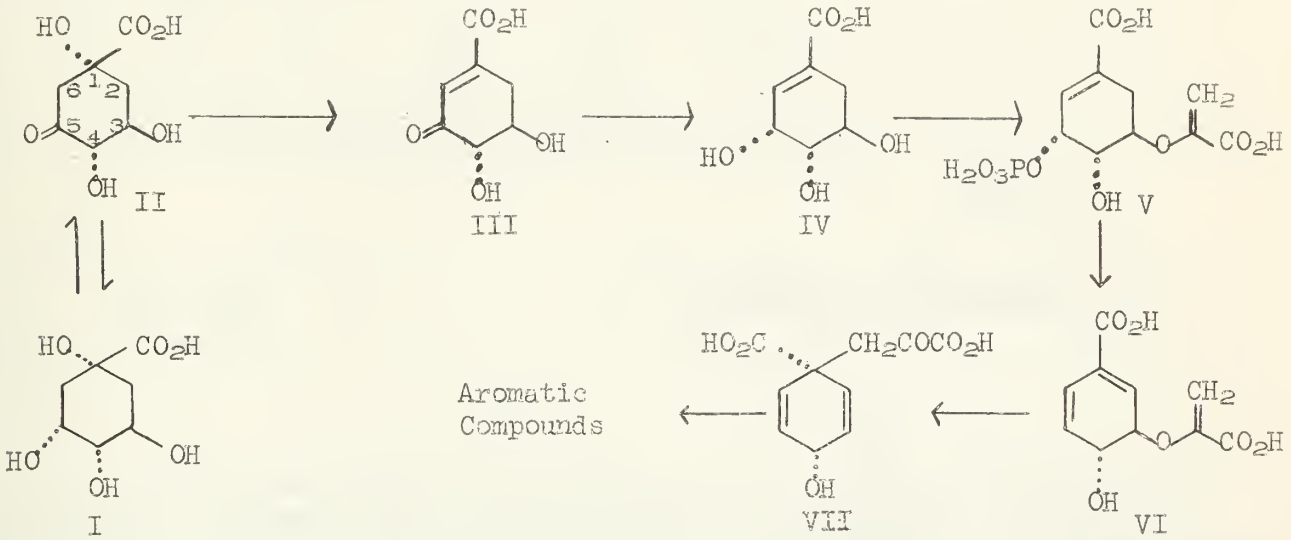
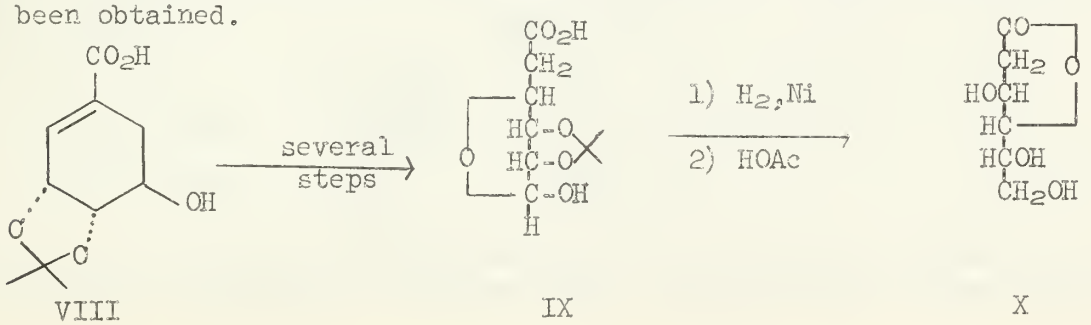


Fig. 1 - Biosynthesis of Aromatic Compounds

Quinic acid is not common in bacteria and is only used when quinic dehydrogenase is fortuitously present to catalyze the conversion to 5-dehydroquinic acid. This outline is simplified and minor pathways and conversions occur from the various intermediates.

An increasing amount of research has also appeared which deals with the organic chemistry of these acids. The purpose of this seminar is to present the structural relationships and syntheses of quinic, shikimic, and prephenic acid and their derivatives.

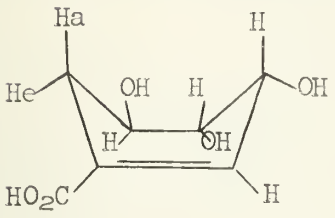
Shikimic Acid.- The relative and absolute configurations of the asymmetric centers and the position of the double bond was established in 1937 by a degradative procedure.[7] A permanganate hydroxylation of the (-)-shikimic acid derivative VIII followed by periodate cleavage and bromine oxidation of the resulting material gave an isopropylidene hemiacetal (IX). Conversion of IX to the known 2-deoxy-D-arabo-hexono-γ-lactone (X) which was also synthesized from 2-deoxyglucose demonstrated the relative relationship of the hydroxyl groups as well as their relationship in an absolute sense to the D-series of sugars. If the double bond had been in the 5,6 position, then the D-lyxo instead of the D-arabo configuration would have been obtained.



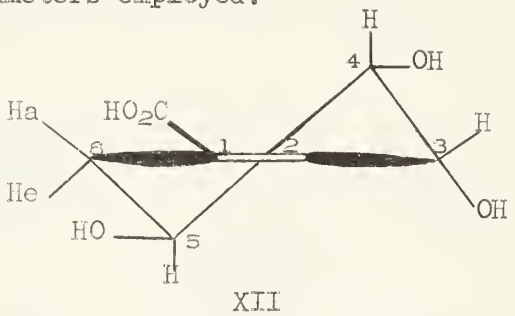
Four extreme conformations are possible for shikimic acid, two half-chair and two boat forms. Comparison of the theoretical dihedral angles (from Barton Models) and the experimental values (from J_{HH} coupling constants and the Karplus equation, $J=J_o \cos^2\phi - .28$) for XI and XII was interpreted to indicate either that on a "time-averaged" basis the half-chair species (XII) makes the major contribution and hence is more energetically favored, or on a "static" basis the conformation is essentially the half-chair with some deformation toward the boat form.[8]

		Dihedral Angles Between Protons			
Conformation		3,4	4,5	5,6a	5,6e
Half-chair		50°	180	170	50
Boat		60	120	180	60
Calcd. from J_{HH}:	a)	46	163	144	39
	b)	48	156	141	42

a) Karplus J_o parameters employed.
b) Carbohydrate adopted J_o parameters employed.



XI



XII

Several investigators[9-12] succeeded in performing total syntheses of (±)-shikimic acid, presumably by procedures which could be adapted to construct a specifically labeled molecule for biosynthetic tracer studies. Smissman (fig. 2)[9,10] and McCrindle[11] published essentially the same scheme, except for minor variations, utilizing a Diels-Alder reaction of trans,trans-1,4-diacetoxy-1,3-butadiene with methyl acrylate to construct the basic ring skeleton. Treatment of XIV with several bases under a variety of conditions failed to effect elimination or epimerization, but pyrolysis at 285° in a vacuum provided XV in high yield. The stereochemistry of the intermediates was reported as shown and was based on the cis pyrolytic elimination reaction. In contrast McCrindle interpreted the configuration of the carboxyl group at C-1 to be cis to the C-2 acetoxy group in XIII and XIV on

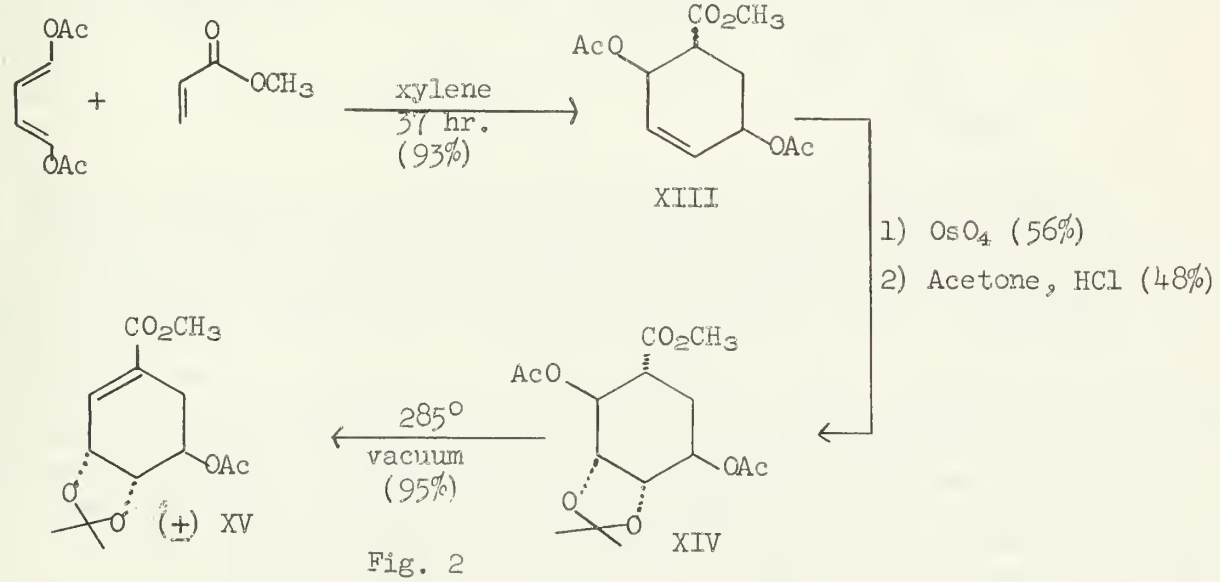


Fig. 2

the basis of Alder rules and because some base catalyzed elimination of acetic acid from XIV was observed (no yield specified). No assurance was made that under the

alkaline conditions epimerization at C-1 had not occurred. Surprisingly, the preferred method of elimination in McCrindle's procedure was also a pyrolysis reaction producing (±)-shikimic acid. It should be noted that quite different conditions were used in the Diels-Alder reaction of each procedure. Both workers resolved the product into the optical isomers by conventional procedures. More recently another synthesis has appeared which utilized a Diels-Alder reaction of 1,3-butadiene and propiolic acid to give 1,4-cyclohexadiene-1-carboxylic acid.[12] Formation of the 4,5-trans-glycol followed by an allylic bromination and acetolysis gave upon hydrolysis a 20% yield of (±)-shikimic acid and lower yields of three epimers.

Quinic Acid.-- Grewe and coworkers, requiring thirteen steps, were the first to perform a total synthesis of (±)-quinic acid.[13] The final reactions are illustrated in fig. 3. Allylic bromination of XVI followed by hydrolysis gave an unsaturated alcohol (XVII). Treatment of XVII with perbenzoic acid provided a sharp melting product in 75% yield which yielded (±)-quinic acid upon hydrolysis. The stereochemistry of the epoxide was rationalized on the basis of product formation by attack and opening at C-5. This assignment was supported more recently in epoxidations which occurred cis to the hydroxyl groups in various cyclic allylic hydroxyolefins, presumably due to some type of association with the epoxidizing reagent.[14]

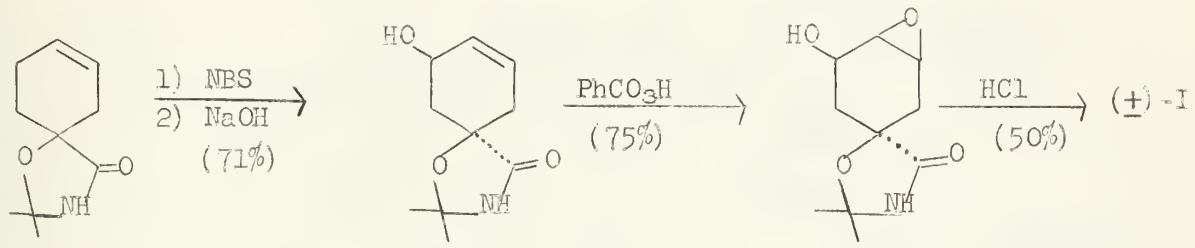
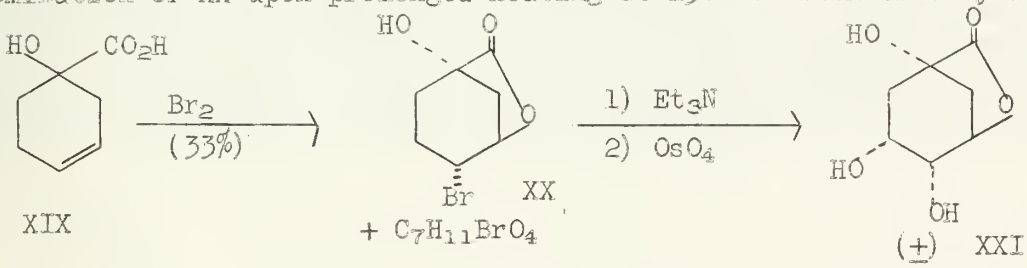


Fig. 3

Recently two reports have appeared on the total synthesis of quinic acid utilizing non-symmetrical intermediates in order to incorporate specific labels in the molecule.[3,15] Wolinsky's procedure is illustrated.[3] Bromo lactonization of the unsaturated hydroxy acid (XIX) gave a mixture of the bromolactone (33%) and an incompletely characterized bromodihydroxycyclohexane carboxylic acid. Dehydrobromination of XX upon prolonged heating at 130-80° with triethylamine in benzene

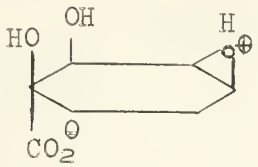


and cis-hydroxylation of the unsaturated lactone with osmium tetroxide afforded a 32% yield of (±)-quinide (XXI) which was identical to an authenic sample.

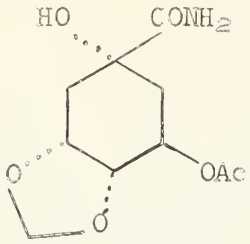
An interesting racemization occurred upon prolonged heating of (-)-quinic acid, (-)-quinide, or (-)-triacetylquinide which was rationalized by reversible formation between the parent compound and a symmetric δ-lactone via an intermediate of the type XXII.[3,13]

Direct conversion of quinic acid into shikimic acid by simple acid catalyzed dehydration was not possible due to the preference of the formation of a γ-lactone, thus creating a bridge-head alcohol at C-1 and preventing elimination. Fischer and Dangschat succeeded by using an indirect procedure.[16] Prolonged treatment of the quinic amide derivative XXIII with p-toluenesulfonyl chloride gave the corresponding α,β-unsaturated nitrile (fortunately with the correctly placed double bond) which was converted to shikimic acid upon hydrolysis. Grewe and coworkers[17] performed a similar conversion by the reduction of the acid chloride of tetracetylquinic acid with $NaBH(OCH_3)_3$ to XXIV in 72% yield. Dehydration of XXIV followed by oxidation

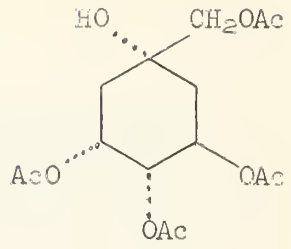
gave triacetylshikimic acid.



XXII



XXIII



XXIV

The conversion of shikimic acid into quinic acid was achieved in over 50% yield[18] (fig. 4). The replacement of the 1-bromo atom in XXV proceeded with a high degree of retention, presumably due to neighboring group participation of the 6-bromo atom or the carboxyl group. The interconversions of quinic and shikimic acid was considered to be indicative of the same configurations about the asymmetric hydroxyl bearing atoms at C-3, C-4, and C-5.

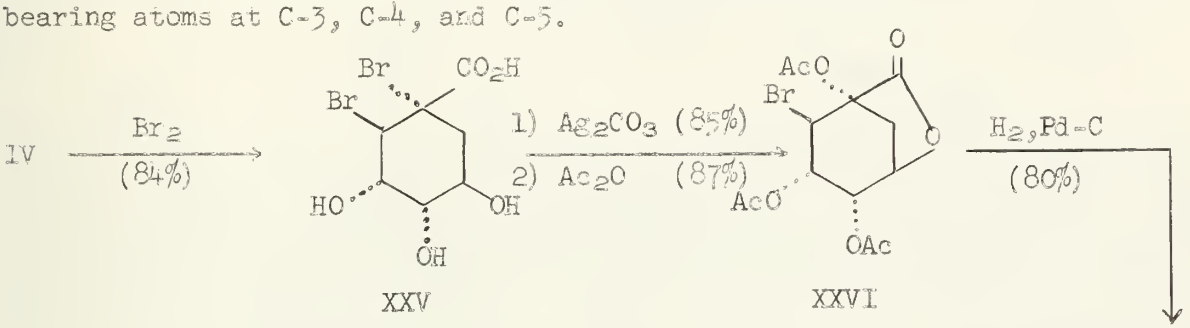
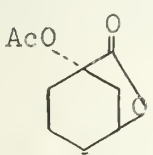


Fig. 4

5-Dehydroquinic and 5-Dehydroshikimic Acid.- 5-Dehydroquinic acid (II) was prepared by nitric acid oxidation[19] or catalytic oxidation[20] (O_2/Pt) of quinic acid in yields of 63% and 44% respectively. This selectivity was rationalized on the generalization that axial hydroxyl groups are more readily oxidized than those occupying equatorial positions. Hydrogenation of III in neutral media followed by acylation gave triacetylquinide and in strongly acidic media the 1,4-diacetoxy lactone (XXVII) was isolated.[19] 5-Dehydroshikimic acid may also be obtained in the nitric acid oxidation of quinic acid if elevated temperatures are employed,[19] or by catalytic oxidation of shikimic acid.[20] Reduction of the methyl ester of 5-dehydroshikimic with $NaBH_4$ gave a 1:1 mixture of shikimic acid and its 5-epimer.



XXVII

Prephenic Acid.- The baruim salt of naturally occurring prephenic acid was found to have an emperical formula of $BaC_{10}H_8O_6H_2O$, to absorb three to four moles of hydrogen upon catalytic hydrogenation, had no ultraviolet absorption between 240 and 260 mu. or infrared absorption at 1485 cm^{-1} typical of "model" aromatic compounds, and was converted to pyruvic acid and carbon dioxide.[21] The structural formula of a 2,5-cyclohexadiene-4-ol derivative (VII) was first proposed on this evidence and confirmed in later studies. Prephenic acid has a plane of symmetry and exhibits no optical activity. However, two isomers (cis and trans) are possible.

In order to determine the correct steric configuration, Plieninger and coworkers synthesized the two possible epimers of tetrahydroprephenic acid (XXX) by the method shown in fig. 5.[22] Both isomers of XXVIII were separated and each converted to the corresponding hydroxydicarboxylic acids.[22,23] Evidence for the correct steric

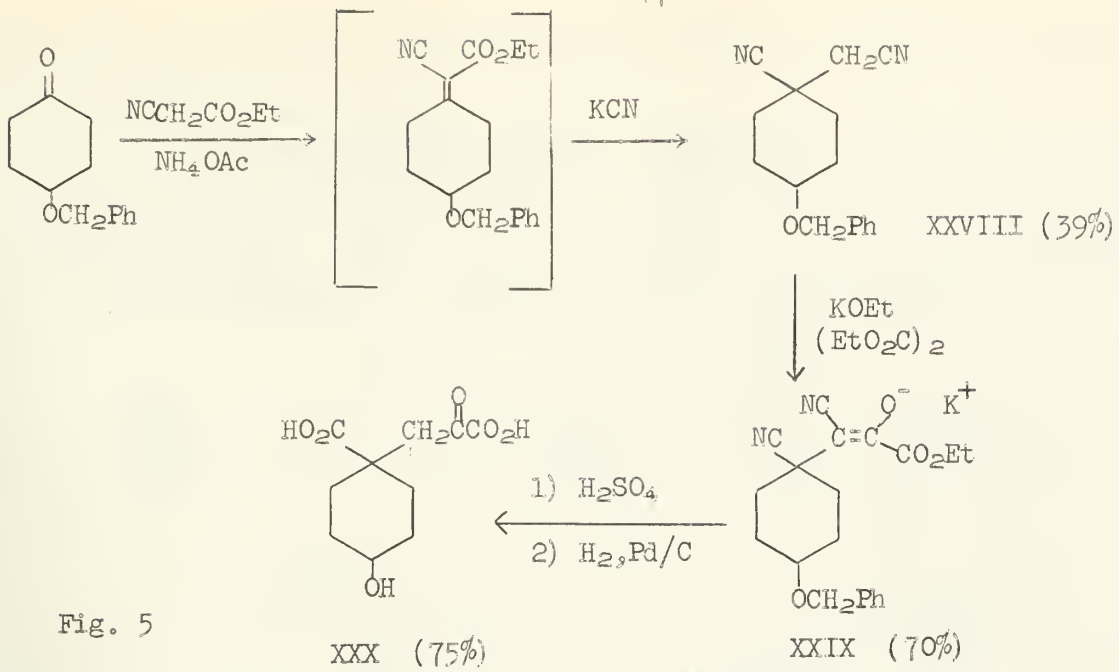


Fig. 5

configuration of these acids was based upon the hydroxyl absorption in the infrared spectra and ease of formation of a bridged lactone. From each epimer of XXVIII was prepared the corresponding tetrahydroprephenic acid as indicated. The correct stereochemistry of the naturally occurring acid was established by comparison of its catalytically hydrogenated product with the synthetic acids and found to have the C-1 carboxyl group cis to the C-4 hydroxyl group. Since only one isomer was obtained from the hydrogenation and not a mixture, then the configuration at C-4 was probably not altered. This steric configuration was also consistent with that predicted for the conversion of chorismic acid[4] (VI) and the 3-enolpyruvate derivative of shikimic acid[25] (V) to prephenic acid.

Prephenic acid was found to be very unstable in acid media and was converted into phenylpyruvic acid (half life: 130 hr., pH 7; 13 hr., pH 6; 1 min., pH 0 at room temperature and 300 min., pH 2; 60 min., pH 1 at 0°).[1,26] It is somewhat more stable in basic media but converted quantitatively into p-hydroxyphenyllactic acid within five minutes in refluxing 2N sodium hydroxide. Two formal mechanisms (fig. 6), both of which involved a hydride shift, were proposed to explain product formation.[26] However, another alternative mechanism is possible which involves a series of tautomeric equilibria and requires no hydride shift.

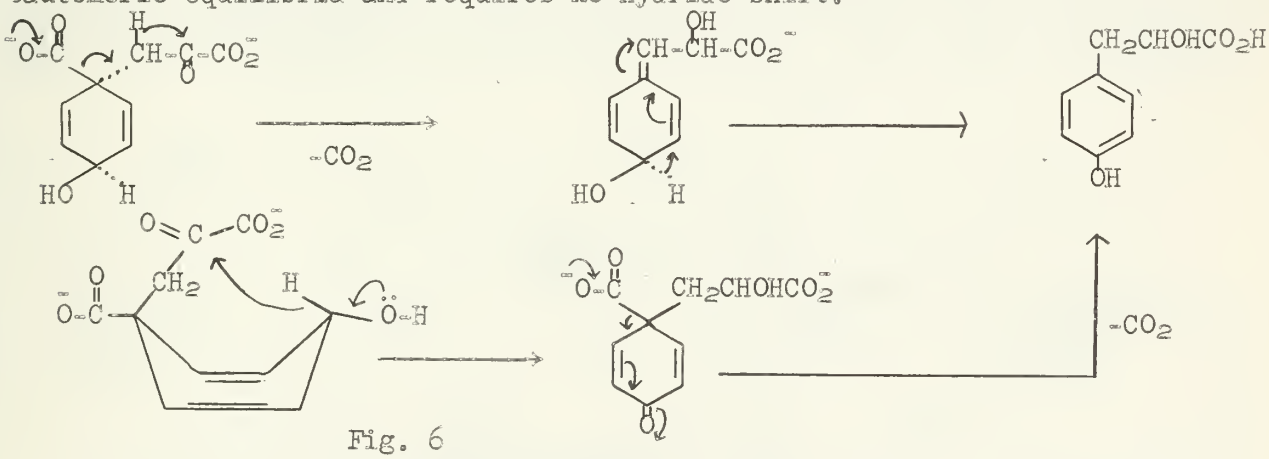


Fig. 6

The synthesis of prephenic acid has presented somewhat of an experimental challenge and to date only limited success has been achieved. The attempted syntheses and interesting model reactions play an important part in the understanding of the problem and are discussed. One must remember the tendency of the final product and many of the intermediates to aromatize in acidic or basic media imposes severe experimental limitations. The general pathway employed has been toward preparation of an

appropriately substituted cyclohexadienone which may be reduced to prephenic acid or a derivative.[26]

The reactions of the model compounds illustrated in fig. 7 are typical approaches utilized in preparing cyclohexadienones. These methods include: (a) dibromination of the saturated ketone (XXX) followed by dehydrobromination with $LiCl-Li_2CO_3$ in dimethylformamide; (b) introduction of a second double bond into the substituted cyclohexenone (XXXII) either via NBS treatment of the enol acetate (XXXIII) followed by dehydrobromination or by a SeO_2 dehydrogenation of the enone; (c) allylic oxidation of the correspondingly substituted cyclohexadiene (XXXIV).[27]

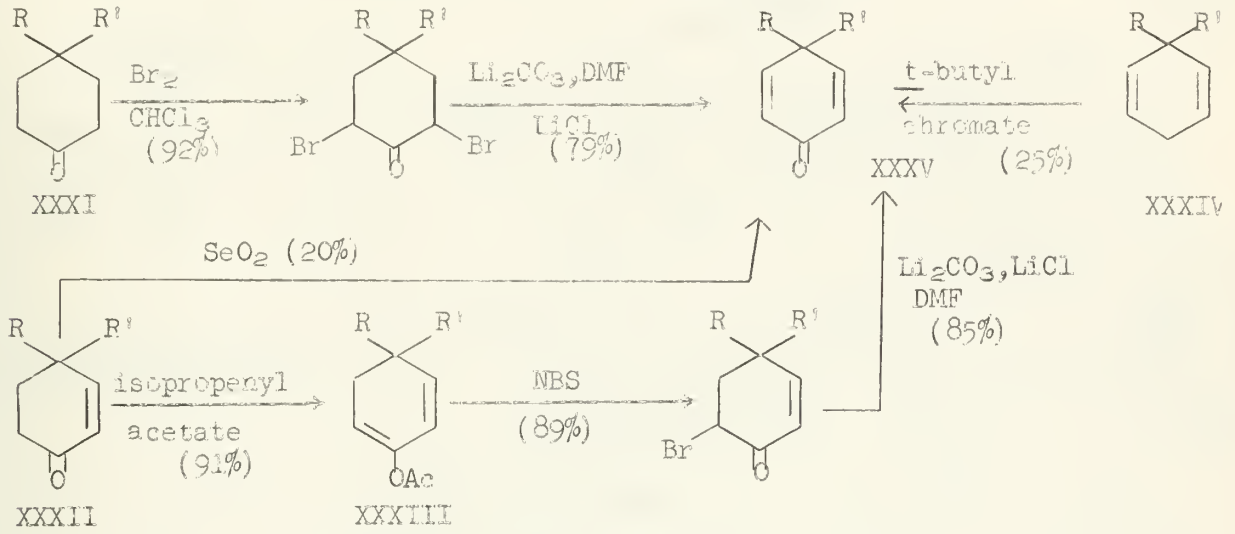
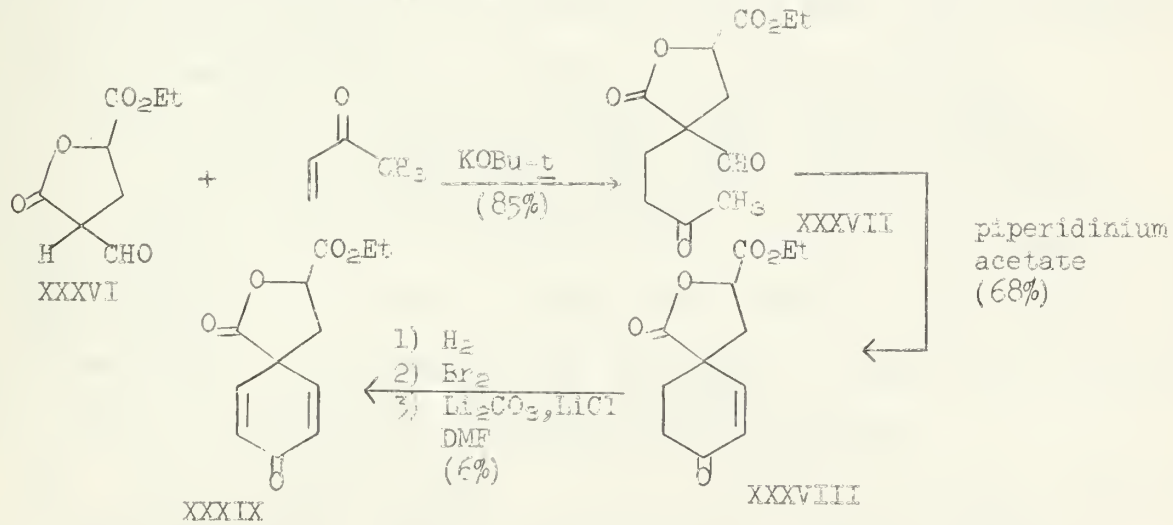


Fig. 7, R= CO_2Et, R'= CH_2CO_2Et

Pathways (a) and (b) are fairly straightforward and provided high yields of the cyclohexadienone (XXXV), except in the case of the SeO_2 reaction. The 1,1-disubstituted cyclohexadiene derivative (XXXIV) was obtained by alkylation of 1,4-dihydrobenzoic acid with chloroacetic acid in potassium amide-liquid ammonia.[28] Allylic oxidation with t-butyl chromate gave XXXV (25% yield), but with lead tetraacetate gave phenylactetic acid.[27,28] Sodium borohydride reduction of XXXV failed, but success was achieved using aluminum isopropoxide to provide an epimeric mixture of the corresponding cyclohexadienols.[26]

The spirocyclic enone (XXXVIII) which was prepared in fairly high yields by a Michael addition of XXXVI to methylvinyl ketone followed by an intramolecular condensation of XXXVII appeared most suitable for the preparation of prephenic acid.[30] Both isomers of XXXVIII were separated. Attempted introduction of a second



double bond via the enol acetate method failed. However, hydrogenation to the saturated analog followed by dibromination and dehydrobromination gave the desired dienone XXXIX in 6% yield plus p-hydroxyphenylacrylic acid

and ester, acetaldehyde, and p-hydroxybenzoic acid. Extensive aromatization and fragmentation occurred upon attempted alkaline saponification and sodium borohydride reduction of the dieneone thus limiting the utility of this procedure.[26]

The procedure which afforded limited success is illustrated in fig. 8.[31,32] Fairly high yields of the various intermediates were obtained. Reduction of the dienone (XL) provided a 1:1 mixture of epimers of the corresponding dienol (XLI) as determined by comparison of its catalytic hydrogenation product with the two synthetic tetrahydroprephenic acids (XXX). Alkaline saponification of the epimeric

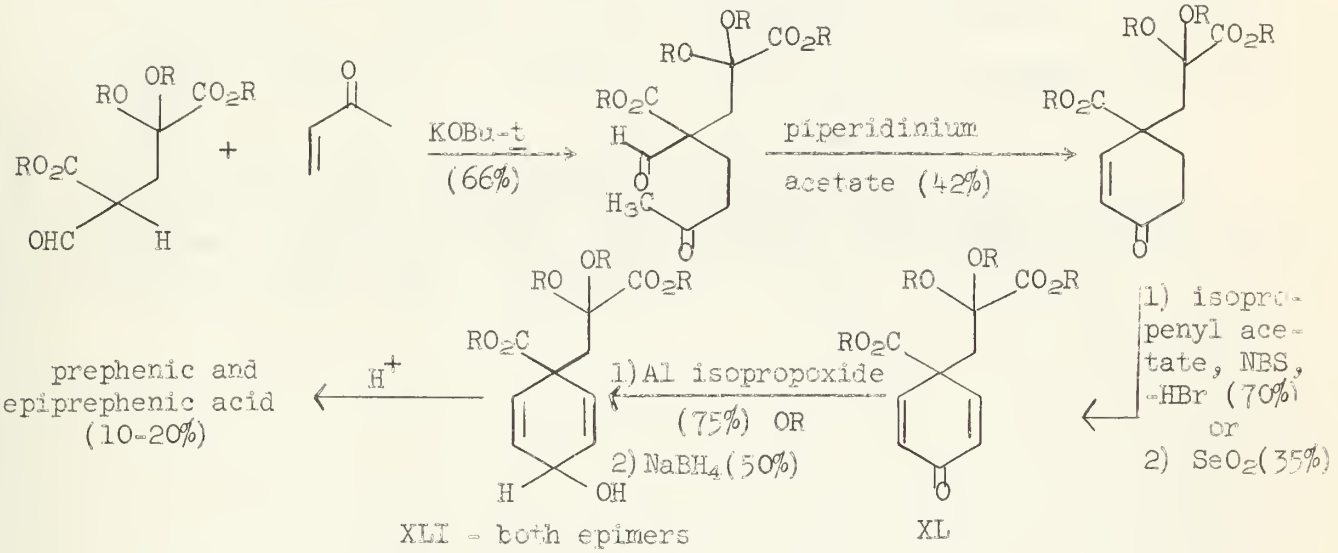


Fig. 8, R=C_2H_5

mixture of dienecls provided a mixture of the acid salts, which was acidified and kept six hours at pH 1.8 at 20°. Competitive ketal hydrolysis and aromatization resulted in a mixture of prephenic acid, epiprephenic acid, and phenylpyruvic acid. After neutralization the prephenates were isolated from a basic ion exchange column and collected as a mixture of their barium salts. The yield varied from 10-20%.

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Cationic Cyclization of Olefins

Reported by Thomas Herrin March 25, 1965

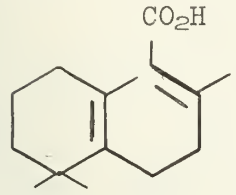
Introduction. Acid-catalyzed cyclization of olefins has long been an active field in organic chemistry.[1] Much of the motivation for this research has come from the hope that knowledge about the detailed mechanism of ring closure in simpler systems would shed light on the biosynthesis of terpenes[2] and related compounds. Although a considerable amount of synthetic and biosynthetic work and elegant theoretical discussions[3,4,5] have been reported on acid-catalyzed ring closure reactions, few rigorous mechanistic studies have been reported until recently.

Cyclization of 2-Δ^3-butenylcyclohexylcarbonium ion. - Linstead and Hibbit found that when 1-methyl-2-Δ^3-butenylcyclohexanol[6] (I) and syrupy H_3PO_4 were heated at 130°, an 89% yield of cis-9-methyl-Δ^2-octalin (II) could be isolated along with a mixture of isomers which were unidentified. Under similar conditions, 2-methyl-1-Δ^3-butenylcyclohexanol[7](III) was dehydrated to a mixture of isomers consisting of mainly 2-methyl-1-Δ^3-butenylcyclohexene (IV) which upon prolonged heating gave a poorer yield of II. The latter could be obtained directly from III in 67% yield if the alcohol was heated at 150° with a mixture of H_3PO_4 and P_2O_5. These results suggested to Linstead that cyclization of I involved loss of water and then cyclization and not formation of IV as an intermediate. Although dehydration of III to give an exocyclic double bond followed by a slow step to give 2-methyl-1-Δ^3-butenylcyclohexene cannot be ruled out from the experimental evidence, it seemed less likely. Further knowledge of this reaction was gained when the dehydration was run in the presence of a nucleophile. When 1-Δ^3-butenylcyclohexanol[8](V) was treated with acetic acid containing small amounts of acetic anhydride and H_2SO_4 at 25°, and the products saponified, a 25% yield of cis-β-decalol (VI) was obtained. The same product was obtained from 1-Δ^3-butenylcyclohexene (VII) under more stringent conditions and in much poorer yields. When 2-methyl-1-Δ^3-butenylcyclohexanol[9] was dehydrated with H_2SO_4 and acetic anhydride and the esters saponified, a mixture of methyldecalols in 55% yield was obtained. These decalols were shown to possess cis ring fusion and to be epimeric about carbon 2. Since the product analysis was not complete and the possibility of trans fused ring compounds being selectively lost in the workup had not been examined, Johnson[17] repeated Linstead's work with butenylcyclohexene making use of vapor phase chromatography for a quantitative analysis. The product composition from a typical experiment was 16% starting material, 13% of a cyclic ether, 1-2% of two additional products, neither of which was trans-Δ^2-octalin, 1.0% of Δ^3-butenylcyclohexanol, 1.8% of an unidentified unsaturated alcohol, 2.8% of an unidentified saturated alcohol which was not identical to any of the β-decalols and 4.4% of cis-syn-2-decalol. The yield of trans-2-decalols was less than 0.3%. The remainder of the total reaction product was evidently water soluble. The possibility of the trans isomer forming water soluble products so as to increase the cis to trans ratio was ruled out by submitting a mixture of cis-syn-2-decalol and trans-syn-2-decalol to the cyclization conditions. The ratio of these products was unaltered. Thus the reaction seemed to progress stereospecifically.

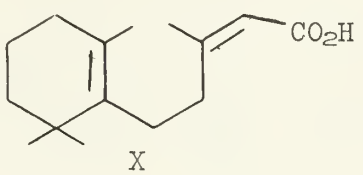
Although Linstead didn't offer a mechanism for the ring closure, in 1951 Stork[10] reported cis products would be expected if proton addition followed by attack of the pi electrons was done in a concerted manner. Similarily in an acyclic trans-1,5,9-triene concerted addition of a proton and ring closure required the trans-decalin system to be formed. Stork hoped to verify these postulates by studying the cyclization of farnesic acid (VIII) and farnesylacetic acid.

Cyclization of Farnesic acid and Related Compounds. - Although Caliezi and Schinz[11] found only bicyclic compounds when farnesic acid was subjected to HCO_2H-H_2SO_4 mixture, Stork and Burgstahler[12] were able to isolate monocyclic acids when milder conditions were used. When farnesic acid was treated with $BF_3 \cdot Et_2O$ in benzene at 5°, a solid crystalline monocyclic acid was obtained in 25% yield. This was shown to be IX. From the mother liquors, a small yield of its geometric isomer X was isolated. The monocyclic acid IX on further treatment with $BF_3 \cdot Et_2O$ in benzene at 40° yielded a bicyclic acid. Under similar conditions, X failed to cyclize but treatment with H_2SO_4-HCO_2H mixture yielded bicyclic compounds. Stork

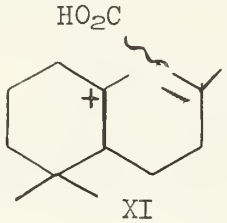
reported the bicyclic acids to be cis-decalin derivatives. Stork and Burgstahler then treated farnesic acid with $BF_3 \cdot Et_2O$ in benzene at 30-35° and found the cyclization proceeded to the bicyclic stage giving a 35% yield of a cis-decalin derivative and smaller amounts of a stereoisomer, epimeric at carbon one. This seemingly disproved the Stork hypothesis. However, two years later Stadler, Schinz, Stork, and Eschenmoser[13] showed these compounds to possess trans ring fusion. However the formation of monocyclic compounds strongly suggested a



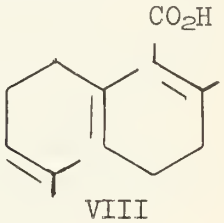
IX



X

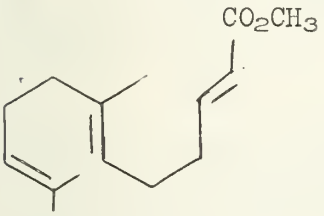


XI

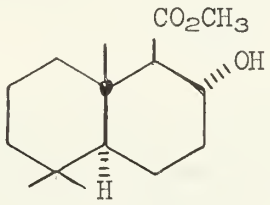


VIII

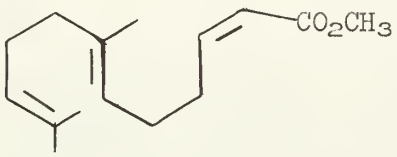
concerted ring closure of both rings was not in operation. Stork did find that the cyclization to the bicyclic acid from farnesic acid did not proceed via an unsaturated monocyclic acid since the latter was harder to cyclize. This suggested the intermediacy of XI.



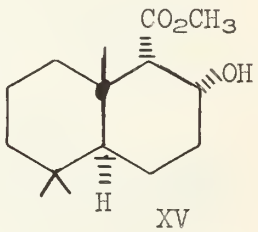
XII



XIII



XIV



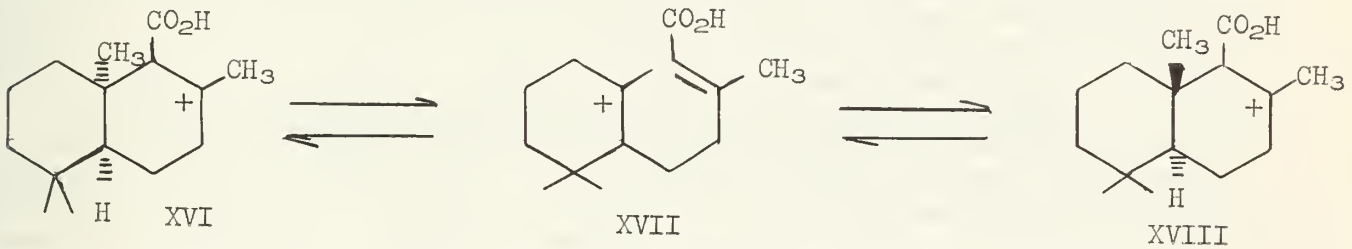
XV

Eschenmoser and coworkers found that when the methyl ester of desmethyl-farnesic acid[14] (XII) was subjected to a H_2SO_4-HCO_2H mixture and the resulting formate esters selectively saponified at room temperature, XIII was obtained in 65-70% yield along with unidentified oils. In a similar manner, XIV underwent ring closure to form XV.

Anti-Planar Hypothesis. - Since in the ring closure of XII there were eight stereoisomers possible, and since XIII was the major product, some stereo-selection was occurring. In order to explain this the anti-planar postulate[15] was developed. The mechanistic requirements for anti-planar cyclization are in principle a synchronous bond formation in which no conformational changes occur or a stepwise ring closure where all carbonium ion intermediates are configurationally stable, (e.g., bridged carbonium ions), followed by sufficiently rapid steps. The stereochemistry of the product is predicted to be different for the two conformations.[16] For example, a chair conformation in the transition state of a trans-trans-1,6-disubstituted-1,5-hexadiene leads to a trans-trans-trans product while a boat conformation leads to trans-cis-trans. Identical results would be obtained if the cationic intermediates were unstable but addition steps proceeded faster than equilibration of the intermediates or where this equilibration occurred but due to steric hindrance, the stereochemistry resulted even though the reaction was not potentially stereospecific.

The formation of trans-decalin derivatives from desmethyl farnesate ester is consistent with antiplanar addition which requires trans ring fusion from the acyclic olefin. (A concerted mechanism however, is not the only means of obtaining trans-decalin derivatives.) Eschenmoser attributes the relative configuration of the ester group in the trans-decalin system not to be the result of a concerted ring closure but rather that the second ring was formed from a chair conformation of the acyclic olefin. However, in showing farnesic acid could be cyclized to the monocyclic compounds, Stork and Burgstahler raised considerable doubt as to whether the cyclization of desmethyl farnesate ester followed anti-planar addition, for

the double bond utilized in the formation of the second ring is more nucleophilic in farnesic acid than in the desmethyl farnesic acid series which should aid a concerted mechanism. Formation of the trans-decalin series could have simply resulted from neutralization of positive charge by equatorial attack of the double bond giving the most thermodynamically stable product. Although Eschenmoser did not report the isolation of a monocyclic compound, he did report that the monocyclic compound gave the bicyclic derivative in about the same yield as from the acyclic olefin. This also suggested XIII and XV were formed in a two step process. But if an unsaturated monocyclic olefin was formed, ring closure proceeded to give the opposite stereochemistry as that found in the Linstead case in which cis-decalin compounds were formed from monocyclic olefins. A possible explanation of this is that the unknown cis compound XVI was actually formed but underwent fragmentation to a monocyclic carbonium ion XVII and then underwent ring closure to the more stable trans-decalin compound XVIII. The intermediacy of XVII can be rationalized to be favored in this case as compared with the Linstead case since the positive



XVI XVII XVIII

charge in XVII is further from the carboxyl group than in XVI or XVIII.

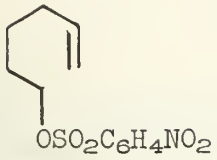
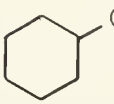
To test this hypothesis, Johnson and coworkers[17] prepared the cis and trans bicyclic compounds. Each was treated with $BF_3 \cdot Et_2O$ in benzene under conditions reported by Stork for the conversion of monocyclic farnesic acid to the bicyclic compound. The products were esterified with CH_2N_2 and analyzed by v.p.c., and no conversion was found. This forced Johnson to another interpretation of the stereochemical process of ring closure in farnesic acid type compounds. Due to conjugation of the double bond with the carboxyl group the double bond lacked the nucleophilicity to cause a concerted ring closure, but rather the process occurred stepwise through XIX.

XIX

Although Stork criticized this because the double bond wouldn't be expected to attack from an equatorial position in a stereospecific manner, Zimmerman[18] has shown in the protonation of the enol of 2-phenylbenzoylcyclohexane, the proton approaches from the equatorial position giving the less stable cis product. This caused considerable doubt about the biosynthesis of natural products from squalene, for ring closure could occur stepwise and not follow anti-planar addition.[19]

Cationic Initiation from Solvolysis Reactions. - In order to gain a more selective cationic initiator, Johnson turned to solvolysis reactions. Bartlett and Clossen had studied the solvolysis of the p-nitrobenzenesulfonates of 4-pentenol and 5-hexenol in acetic acid buffered with sodium acetate. They found that the former compound solvolyzed slower than the corresponding n-hexyl p-nitrobenzenesulfonates while the latter showed a 50% rate increase, and a 25% yield of cyclic products could be isolated. Since it is known that formic acid[20] is more effective in the anchimerically assisted solvolysis of phenylethyl tosylate, Johnson[21] repeated the solvolysis of 5-hexenyl p-nitrobenzenesulfonate in formic acid. The solvolysis rate was approximately twice that of the n-hexyl sulfonate and more cyclic product resulted than when acetic acid was used. The solvolysis of 5-hexenyl p-nitrobenzenesulfonate was run in varying concentrations of formic acid with varying amounts of sodium formate. The results are summarized in Table I. As the concentration of formic acid dropped, the ratio of cyclohexanol to hexenol fell. Lowering the concentration of formate improved the ratio only slightly.

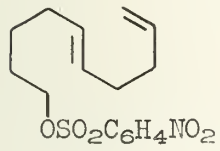
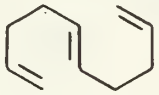
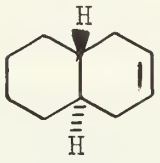
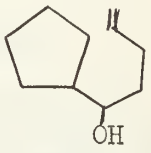
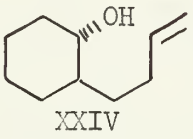
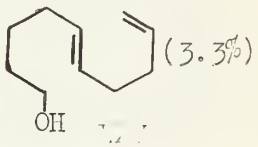
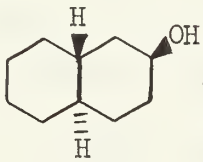
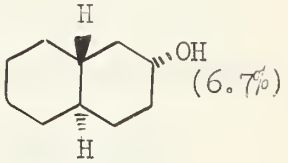
Table I

reactant	conditions	products (relative amounts) after hydrolysis
	100% HCO_2H HCO_2Na	 (51%)  (24%)  (4%) 20% other hydrocarbons

Formation of 5 and 7 Membered Rings. - Formolysis of 4-pentenyl p-nitrobenzenesulfonate gave no detectable amount of cyclic compound. Formolysis of 6-heptenyl p-nitrobenzenesulfonate proceeded at about the same rate as the n-hexyl ester and gave only traces of cyclic compound. In all experiments it was necessary to buffer the solution in order to limit undesirable reactions.

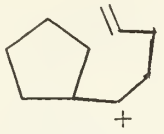
Solvolysis of trans- and cis-decadienyl p-nitrobenzenesulfonates. To further test the anti-planar hypothesis, the solvolysis of trans-5,9-decadienyl p-nitrobenzenesulfonate (XX) was studied. The solvolysis of XX produced a mixture of nine components and an unidentified fraction of hydrocarbons. The results are summarized in table II. The most important fact from this experiment was that the

Table II

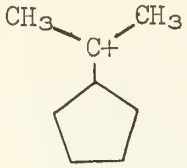
reactant	conditions	products (relative amounts) after saponification
	80% HCO_2H HCO_2Na	 (trace) VII (5.4%) XXI  (2.9%) V (1.6%)  (14%) XXII XXIII  (51.2%) XXIV  (3.3%)  (2.2%) XXVI  (6.7%) XXVII

bicyclic compounds were entirely trans-decalin derivatives as would be expected from a concerted ring closure of the trans acyclic diene. The formation of a five membered ring was unusual since none was found in the solvolysis of 4-pentenyl p-nitrobenzenesulfonate. In the latter case ring closure was unfavorable because of the position of the double bond, and the destabilization of the cyclopentylcarbonium ion due to constraint of the preferred 120° bond angles. However, in the formation of Δ^3-butenylcyclopentylcarbinyl cation (XXVIII), the positive charge was exocyclic and the preferred bond angles were allowed. Similarly solvolysis of 5-

isooctenyl tosylate gives the relatively stable exocyclic tertiary cyclopentyldimethyl carbonium ion (XXIX) upon closure to a five membered ring.[22]



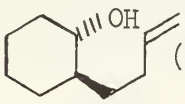
XXVIII



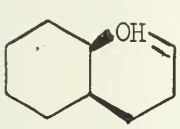
XXIX

Although the bicyclic compounds from solvolysis of XX are exclusively trans-decalin derivatives, the reaction may be potentially nonstereospecific. Trans products would be expected from equatorial attack of the pi electrons in 2-Δ^3-butenyl-cyclohexyl carbonium ion (XIX). To clarify this problem, Johnson and coworkers[23] examined the solvolysis of cis-5,9-decadienyl p-nitrobenzenesulfonate (XXX). If XIX was a common intermediate in both solvolytic reactions, identical products would be expected. A 0.02 M solution of the sulfonate esters, XX and XXX, were solvolyzed in anhydrous formic acid containing pyridine (0.04 M) for one hour at 75°. The formate esters were cleaved with $LiAlH_4$, and the products analyzed by v.p.c.. The results of the solvolysis of XX and XXX are summarized in table III and IV respectively.

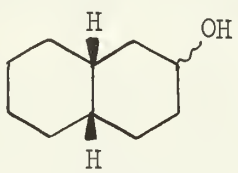
Table III

reactant	conditions	products (relative amounts) after $LiAlH_4$ treatment
XX	100% HCO_2H 0.04 M pyridine 75°	V (3%) XXIII (10%)  (57%) XXV (8%) XXIV XXVI (5%) XXVII (14%) 3% total of unidentified components

There was no detectable amount of cis monocyclic alcohol XXXI or the cis-decalols XXXII among the products of the solvolysis of XX. The results were comparable to those found in 80% formic acid. The results of the solvolysis of XXX are given in Table IV. There was no detectable amount of the trans monocyclic alcohol or the trans-decalols among the products from the solvolysis of XXX. Since the reaction products from the two sulfonate esters possessed different stereochemistry, XIX cannot represent a common intermediate. The strong similarity in product distri-

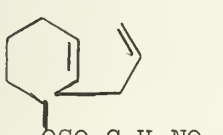
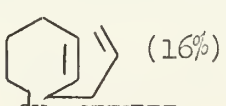


XXXI



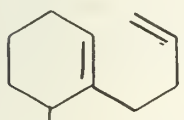
XXXII

Table IV

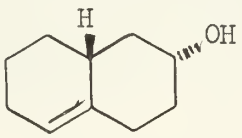
reactant	conditions	products (relative amounts) after $LiAlH_4$ treatment
 $OSO_2C_6H_4NO_2$ XXX	100% HCO_2H 0.04 M pyridine 75°	V (3%) XXIII (8%) XXXI (56%)  (16%) (13%) OH XXXIII XXXII 4% mixture of unidentified components

bution suggested to Johnson a common mechanism may have been operating, that is, the cyclization must consist of concerted processes or cationic intermediates capable of retaining their stereochemistry.

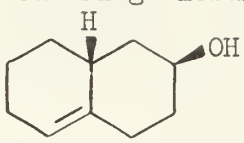
Allylic Cation Initiators. - Since the conditions necessary to promote anchimerically assisted solvolysis of primary sulfonates are strenuous, a more stable cationic site which could be formed under milder conditions was desirable. For this purpose, Johnson[24] considered allylic cations. Another desirable feature is the potential reversibility of formation of an allylic cation after once being captured by a nucleophile in contrast to the solvolysis of primary sulfonates. These objectives of obtaining cationic sites under mild conditions to give high yields of cyclic product were realized with 2-Δ^3-butenyl-Δ^2-cyclohexenol (XXXIV). This alcohol cyclized readily, the reaction being completed in 5 minutes when done in anhydrous formic acid at room temperature. When the esters were saponified and the products analyzed by v.p.c., the following compounds and their relative amount were: 92% syn-$\Delta^{1,9}$-6-octalol (XXXV), 6% anti-$\Delta^{1,9}$-6-octalol (XXVI) and 2% olefins. The actual yield (after correction for impurities in the starting material) was between 80 and 90%. The stereoselective formation of XXXV may have arisen by rapid ionization to the allylic carbonium ion XXXVII followed by a synchronous ring closure and



XXXIV

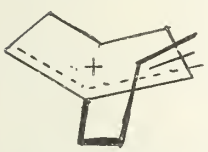


XXXV

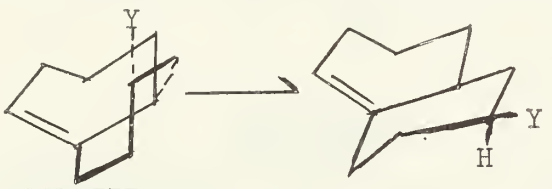


XXXVI

attack by a nucleophile Y as pictured in XXXVIII. An alternative mechanism would be a stepwise formation of the secondary carbonium ion XXXIX and then attack by Y from the favored equatorial position. A third mechanism would be synchronous ionization and cyclization.[25] However, in the cyclization of XL and XLI, the evidence



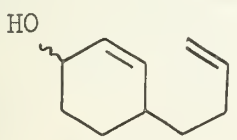
XXXVII



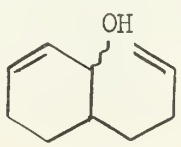
XXXVIII XXXIX

suggested (but does not prove) that the latter mechanism was not operating. If there were ionization to the allylic cation followed by ring closure both XL and XLI would have a common intermediate, and products and relative amounts must be the same.

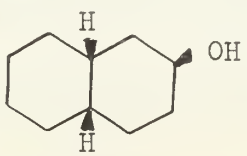
To test this idea XL and XLI were prepared (in both cases an epimeric mixture was used). When the dienols, XL and XLI were treated with HCO_2H-H_2SO_4 mixture at room temperature, the reaction was about 90% complete in 5 minutes. The esters were cleaved with $LiAlH_4$ and the v.p.c. analysis of the octalols showed that the major alcohol was obtained in about a 92% relative yield and was the same with both dienols. This crude mixture of octalols was hydrogenated over palladium-on-carbon and then analyzed by v.p.c. The absolute yield of alcohol (after hydrogenation) from the dienol XLI was 56% of cis-anti-2-decalol (XLII), 5% of trans-syn-2-decalol (XXVII), and no trans-anti-2-decalol (XLIII). The yield from dienol XL was 68% XLII, 10% XXVII and 3% XLIII. The primary product from ring closure showed absorption for two vinylic protons in the n.m.r. spectrum, thereby ruling out a double bond at a bridgehead. The octalol upon oxidation with Jones reagent gave



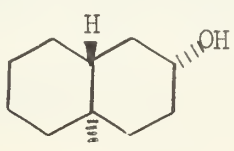
XLI



XL

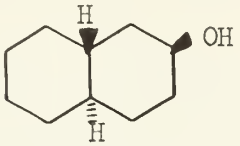


XLII

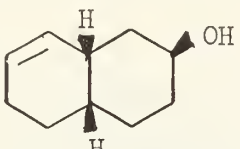


XXVII

a ketone which formed a yellow (unconjugated) 2,4-dinitrophenylhydrazone. This evidence and by chemical analogy (barring double bond migration) supported structure XLIV for the octalol. Within the limits of experimental error, the products and

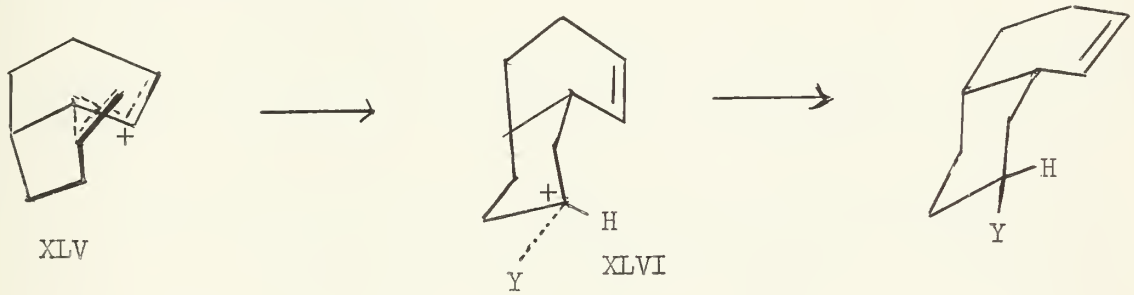


XLIII



XLIV

relative amounts were the same for both dienols. Johnson took this as support for the intermediacy of an allylic cation XLV (this by no means proved its existence). The high degree of stereoselectivity of the cyclization to form XLIV in good yield was unexpected. The formation of the cis-anti isomer precluded a concerted trans addition of the nucleophile to the olefinic bond for it would have led to the syn series. The results suggested a stepwise process with the intermediacy of a cation like XLVI. Dreiding models suggest better overlap of the allylic cation and terminal double bond is possible when the intermediate monocyclic cation is in a conformation leading to cis rather than to trans. Johnson suggested this as an explanation for the stereo-electronic factor leading to cis products. If XLVI is the intermediate, equatorial attack must occur on XLVI rather than on its flipped form to give the observed products.



XLV XLVI

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THE CONJUGATIVE EFFECTS OF CYCLOPROPANE

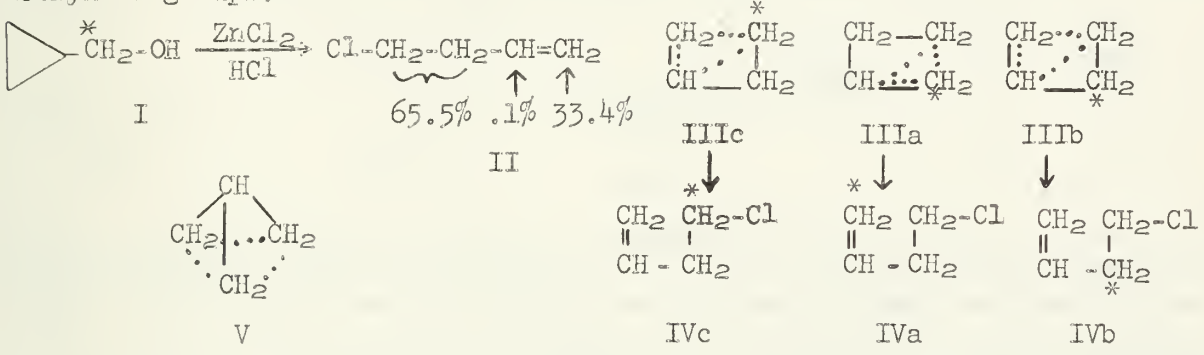
Reported by Jack Timberlake April 5, 1965

The unique nature of the cyclopropane ring has lured many workers into the study of its chemistry.[1-6] Several predictions on its structure and bonding have been worked out,[7] and the majority of opinion is that cyclopropane is unparalleled by other cycloalkanes in its unusual stabilizing effect. This unprecedented nature has been attested kinetically, spectroscopically (UV, IR, Raman, and NMR), by dipole moment studies, boiling point comparisons, heats of combustion and others.

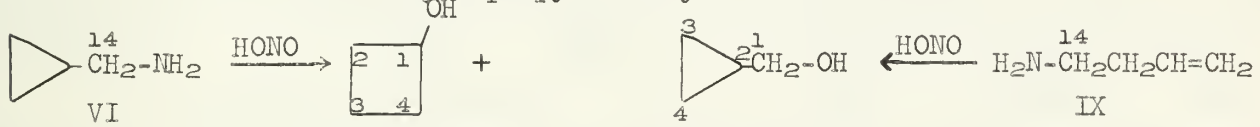
As there is contrariety in the literature, it is the purpose of this seminar to re-examine the conjugative ability of cyclopropane.

The most significant early work was done by J. D. Roberts. He found abnormally large solvolytic reactivities for cyclopropylcarbinyl and cyclobutyl halides and sulfonate esters[8] and was led to postulate non-classical intermediates. The carbonium ion-type reactions gave similar product mixtures whether one started with cyclopropyl or cyclobutyl substrates. This suggests that such reactions go through common cationic intermediates and that the small observed variation in product composition is due to specific influences and not drastic changes in mechanism. The now famous equilibrating non-classical bicyclobutonium ions (III a-c) were proposed as the reactionary intermediates.

As a test for the equilibration, cyclopropyl carbinol-α-^{14}C (I) was treated with $ZnCl_2$ and HCl.[9] The final product, allylcarbinyl chloride (II), is thermodynamically stable under the reaction conditions. If equilibration of IIIa-c is complete before II is formed, the allyl chloride will have ^{14}C distributed equally between the three methylene groups.



If no energy barrier exists for interconversion between IIIa-c, then a symmetric "tricyclobutonium" ion V can be imagined. The isotopic distribution in II does not allow one to distinguish between IIIa-c and V. If, however, a reaction can be found where IIIa-c equilibriate slower than they react with solvent, their existence can be inferred. By examination of IIIa-c it can be seen that conversion of IIIa to IIIb is more easily accomplished (less distortion of the atoms) than is conversion of either IIIa or IIIb to IIIc. That IIIc is a higher energy intermediate is in accord with data from deamination of cyclopropylcarbinyl amine-α-^{14}C VI.



carbon atoms	1	2=4	3
VII	0%	35.8%	28.1%
XI	0%	31.6%	36.8%

carbon atoms	2+3+4	1
VIII	48.3%	53.2%
X	70.4	29.2

To obtain C^{14} in the three position of cyclobutanol requires attack of solvent at the three position in IIIc.

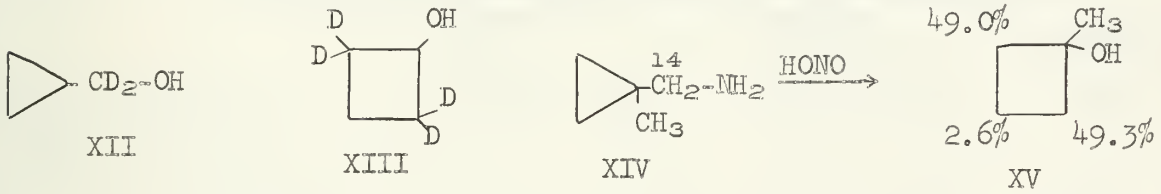
The different degrees of shuffling of methylene groups in the two products, VII

and VIII could be explained by an opposing S_2 type reaction on the diazonium ion of VI. To establish this Roberts[10] decided to approach the equilibrium from a different direction. By deaminating allylcarbinyl-α-^{14}C amine (IX), the "hot" carbonium ion could be avoided as "the diazonium ions would lose most if not all of their sizzle by the time they undergo ring closure to yield the intermediates". Furthermore, ion IIIb would be expected to form first, rather than IIIa which is presumably formed from deamination of cyclopropylcarbinyl-α-^{14}C amine.

Examination of X and XI shows that the average extent of isotope position rearrangement appears to be somewhat greater than found previously. Similar results have been reported in the formolysis of allylcarbinyl tosylate labeled with deuterium.[11] The rate of solvolysis was greater than for the saturated analog and the distribution of the deuterium in the products was close to statistical. It should be mentioned, however, that this proof is less rigorous than previous ones, for the labeling in products is clouded by the fact that some of the initial products are unstable under the reaction conditions. Hence, part of the scrambling could be due to rearrangement to the thermodynamically stable allylcarbinylcarbinol product.

Brown,[12,13] from his work on solvolysis of cyclopropylcarbinyl chloride in ethanol coupled with the results of product studies by Bergstrom[14] on cyclopropylcarbinyl benzenesulfonate, concluded that derivatives may solvolyze by way of a cationic intermediate without formation of a rearranged product and that the enhanced rate of solvolysis may not be due to any driving force from formation of a non-classical cation.

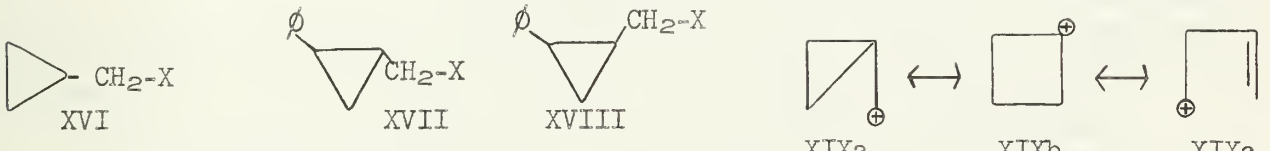
Roberts[15] has shown that Brown's inference that unrearranged products are not formed in solvolysis of cyclopropylcarbinyl chloride is wrong. He found that a nearly statistical distribution of deuterium appears in the products cyclobutylchloride and cyclopropylcarbinyl chloride from treatment of XII and XIII with $SOCl_2$.



XII XIII XIV XV

Thus the three methylene groups of cyclopropyl carbinol and cyclobutanol achieve near equivalence during the reaction. To distort this equivalence Roberts put methyl groups in the one position of the cyclopropyl ring, and demonstrated its expected rate increase for the solvolysis of the chloride.[16] The label distribution in the product of deamination of amine XIV[17] is shown in XV and is rationalized from the Hammond[18] postulate. It is the kinetic product arising from attack of solvent at the position of highest charge concentration.

Similar results have been reported by Sneen,[19] who found that the solvolysis of cyclopropylcarbinyl-β-naphthalene sulfonate (XVI) was intermediate in rate between the faster trans-2-phenylcyclopropylcarbinyl (XVII) and the slower cis- compound (XVIII). His conclusion was that if Robert's bicyclobutonium ion is represented by



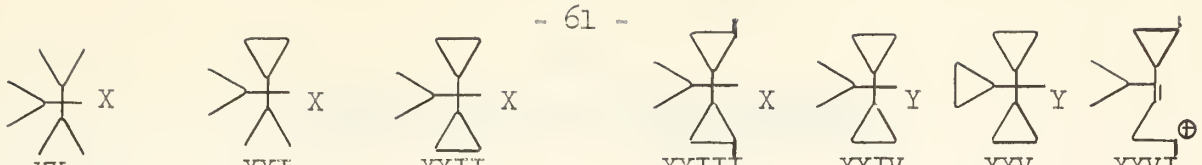
XVI XVII XVIII

X=β-naphthalenesulfonate

XIXa XIXb XIXc

the three valence bond resonance hybrids XIXa-c then structure XIXc contributes only in a minor way.

Perhaps the most striking solvolysis reactions that lend themselves to the conjugative interpretation are those found by Hart[20-22] for the solvolysis of XX-XXV. The relative rate results are even more astonishing when one considers that: a) cyclopropyl groups are less sterically demanding, b) cyclopropyl is considered to be electron withdrawing inductively[23-25] and c) the products contain unrearranged alcohols and thus the rate does not involve a release of ring strain. The fact that



XX XXI XXII XXIII XXIV XXV XXVI

	XX	XXI	XXII	XXIII	XXIV	XXV
relative rates	1	246	23,500	124,000	1	1080

X= p-nitrobenzoate Y= Benzoate

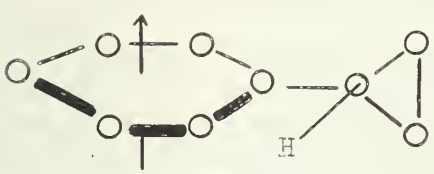
no rearranged products are formed does not rule out bicyclobutonium ions as intermediates. It is interesting that the rate enhancement of XXIII over XXII is interpreted as being indicative of a contribution from XXVI, a form similar to XIXc that Sneen ruled out as a major contributor. An interesting study of tricyclopropyl carbonium ion has been conducted by Deno[26,27] who found that the NMR of this carbonium ion in trifluoroacetic acid gave rise to a single sharp peak at 2.26 ppm. The fact that the β methylene protons are shifted downfield to a larger degree than the α-methine protons, and that the tricyclopropyl carbinol can be recovered unchanged is excellent evidence for cyclopropyl delocalization.

In 1958, Trachtenberg[28] concluded that the cyclopropyl ring was unable to transmit conjugation, when he found the ρ value for the ionization of phenylcyclopropylcarboxylic acid in water was slightly smaller than ρ for β-phenylpropionic acid. However, Fuchs and Bloomfield[29] found that changing the solvent system from water to 50% ethanol produced a pronounced change in the transmission of electrical effects. In this case both cis-and trans-cyclopropylcarboxylic acid show greater ρ values than β-phenylpropionic acid.

TABLE 1

ρ-VALUES FOR ACID IONIZATION AND ESTER HYDROLYSIS

	ρ-acid[28] water	ρ-acid[29] 50% Ethanol	ρ-Ester hydrolysis[30-31] 87% Ethanol
β-phenylpropionic	0.204 ± .007	0.344 ± .023	0.591 ± .032
trans-2-phenylcyclopropane carboxylic	.182 ± .014	.473 ± .018	.812 ± .019
cis-2-phenylcyclopropane carboxylic	——	.436 ± .028	1.02 ± .029
trans-cinnamic	.466 ± .04	——	1.314 ± .023
cis-cinnamic	.643	——	1.12 ± .04



XXVII

Presumably a change from water to a less polar medium acts to diminish solvation of the carboxylate ion relative to the carboxylic acid, thus increasing the free energy of ionization and thereby calling upon a greater electrical demand from cyclopropane.

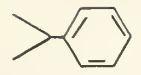
It is believed that in conjugation with π systems the cyclopropane ring has a preferred configuration in which overlap will be maximized. This confirmation can be illustrated with phenylcyclopropane (XXVII). In this maximized situation the benzene ring is in the same plane as the C-H methine bond but the benzene ring is perpendicular to the cyclopropane ring. In this manner the p orbital from carbon on benzene can overlap with the "bent bond" p orbitals of cyclopropane.

Several Russian workers[32] have done extensive Raman spectroscopy studies on cyclopropane derivatives. In these studies the double bond asymmetric stretching vibration of the phenyl rings at approximately 1600 cm^{-1} is observed and its integral intensity compared to a model compound. Intensity, in units/mole, is expressed relative to a standard sample of cyclohexane whose absorbtion at 802 cm^{-1} is assigned the integral intensity value of 500 units/mole.

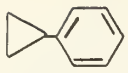
From table 2, it can be seen that the intensity is increased on going from isopropyl to cyclopropyl to isopropenyl benzene as one would expect if integral intensity is a true measure of propensity to conjugate. Levina has calculated that for a cyclopropyl group to have the preferred conformation (XXVII) in

TABLE 2

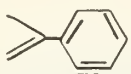
RAMAN INTENSITIES OF ALKYL BENZENES



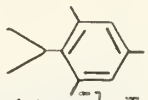
$\Delta\nu cm^{-1}$ I∞
1606 380



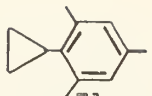
$\Delta\nu cm^{-1}$ I∞
1607 920



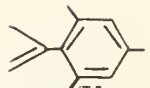
$\Delta\nu cm^{-1}$ I∞
1600 2000



$\Delta\nu cm^{-1}$ I∞
1609 487



$\Delta\nu cm^{-1}$ I∞
1612 532

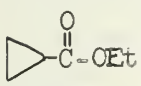


$\Delta\nu cm^{-1}$ I∞
1612 2665

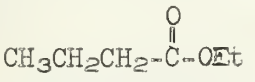
XXVIII

cyclopropylmesitylene (XXVIII), the methylene hydrogens of cyclopropane and the methyl hydrogens would be separated by only 0.8 Å. Therefore, the actual configuration (XXVIII) would be one in which the methine hydrogen of cyclopropane is approximately perpendicular to the benzene ring. One is led to believe this is the case on comparing isopropyl to cyclopropylmesitylene, for the increase in intensity is slight. It is hard to comprehend then, why the same requirements would not be imposed on isopropenylmesitylene. The latter result casts serious doubt on these Raman studies as evidence for or against conjugation.

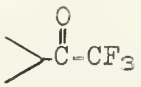
On the surface, infrared studies appear more reliable, although differences are small and therefore can't be extrapolated with great precision from one work to another. Ethylcyclopropyl carboxylate (XXIX) has been reported to absorb at 1730 cm^{-1} while ethylbutanoate (XXX) absorbs at 1738cm^{-1}.[33] Isopropyltrifluoromethyl ketone (XXXI) absorbs at 1750 cm^{-1} while cyclopropyltrifluoromethyl ketone (XXXII) absorbs at 1766 cm^{-1}.[34] Conjugation is normally thought to cause a shift to longer wavenumbers and apparently this is what is being observed. In all these cases the -I inductive effect of cyclopropane relative to other alkyl groups, which would be expected to cause a shift to longer wavelength, is being overpowered by the conjugative effect of the cyclopropane ring.



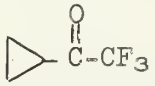
XXIX



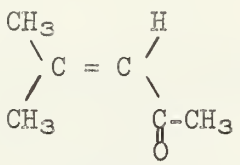
XXX



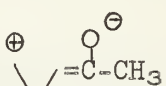
XXXI



XXXII



XXXIII

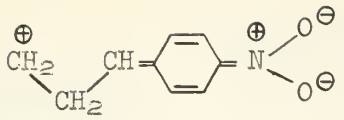


XXXIV

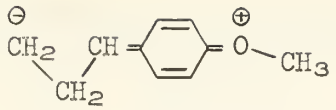
Much of the earlier ultraviolet work has been reviewed[2] and won't be covered here.

Kosower[35] observed that the position of the $\pi \rightarrow \pi^*$ band for methylcyclopropyl ketone could be linearly correlated with Z values for different solvents. Z values are defined as the transition energy, E_t, in kcal/mole, for the charge transfer band of 1-ethyl-4-carbomethoxypyridinium iodide in a given solvent. Since the position of the band varies depending upon the solvent, Z values are a measure of the polarity of the solvent. The variation of the band of methylcyclopropyl ketone upon changing solvents is thought to be due to an interaction of the more polar solvent with delocalized species, thus bringing about a lowering of the excited state transition energy. A change in solvent from isooctane to water brought about a change in ΔE_t=4.5 kcal/mole. This can be compared to a 6.1 kcal/mole ΔE_t change for mesityl oxide for the same solvent systems, and to acetone whose spectrum changes only very slightly. This is thought by Kosower to be due to an interaction such as XXXIV.

Work done by Strait and Ketcham[36] on p-substituted phenylcyclopropanes has shown that cyclopropane acts very strongly as an electron donor in conjugation but as an electron acceptor conjugation is virtually absent. The fact that p-nitrocyclopropylbenzene (table 3) absorbs at a longer wavelength than p-nitrotoluene is thought to be a result of contributions such as XXXV. It is noted that there is no marked difference between p-methoxytoluene and p-methoxycyclopropylbenzene, thus ruling out any significant contribution from XXXVI.



XXXV

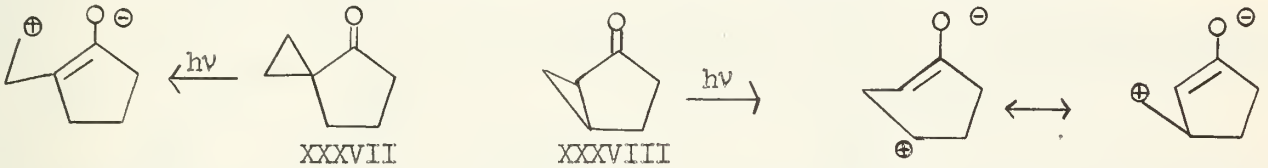


XXXVI

TABLE 3
UV DATA ON ARYLCYCLOPROPANES

	p-x-C_6H_4-y					
	X=H		$X=OCH_3$		$X=NO_2$	
Y	λ max mμ	$\epsilon x10^{-3}$	λ max mμ	$\epsilon x10^{-3}$	λ max mμ	$\epsilon x10^{-3}$
cyclopropyl	220	8.4	225	7.5	280	11.0
methyl	206	3.2	223	7.7	264	10.4

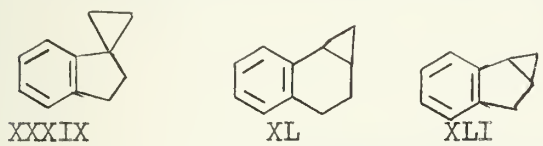
In an effort to gain more insight into the nature of the preference of geometry for conjugation by cyclopropane, Kosower[37] compared the spectrum of spiro-[4.2] heptan-1-one (XXXVII) with that of bicyclo-[3.1.0] hexan-2-one (XXXVIII).



XXXVII XXXVIII

While XXXVII has the preferred configuration, i.e. cyclopropyl group is perpendicular to the plane of the carbonyl group, XXXVIII is twisted out the preference approximately 20°. Preference of configuration not considered, it would be expected that the $\pi \rightarrow \pi^*$ transition energy for XXXVIII would be several kcal/mole less than for XXXVII because the positive charge in XXXVIII should be more readily stabilized than in XXXVII (secondary and primary carbonium ions vs. two primary). However, the observation is that E_t for XXXVII is 5.1 kcal/mole less than for XXXVIII thus leading to the interpretation that XXXVII is geometrically more favorable for the electronic transition.

Eastman and Goodman[38] recently reported results contradicting those found by Kosower. They prepared four different compounds (phenylcyclopropane, spiro-[cyclopropan-1.1-indan] (XXXIX), tetrahydrocyclopropanaphthalene (XL), and tetrahydrocyclopropindene (XLI)) and compared their ultraviolet spectra.



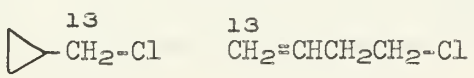
XXXIX XL XLI

Examination of models shows that XXXIX has the cyclopropane ring locked perpendicular to the plane of the benzene ring, i.e. in the preferred conformation. XL, in its most stable arrangement, is about 10° from having the two rings perpendicular and XLI is about 25° out of mutual perpendicularity. The fact that the four spectra are almost identical is taken as evidence that there is no preferred geometry for conjugation of the cyclopropane ring with a benzene ring.

Although it is reasonably safe to assume that a positive charge developed on a carbon adjacent to a cyclopropane ring is stabilized by the ring, the amount of stabilization imparted to a free electron or to an anion is harder to assess.

Roberts[39] has found that in the vapor phase chlorination of cyclopropyl-C^{13}-methane the major products XLII and XLIII, formed in a ratio of 2:1, had only the isotopic distribution shown. The lack of isotope position rearrangement and the conspicuous failure of cyclobutyl chloride to be formed argues against the intervention of a bicyclic bridged radical. Walling has reported similar results for liquid phase chlorination.[40]

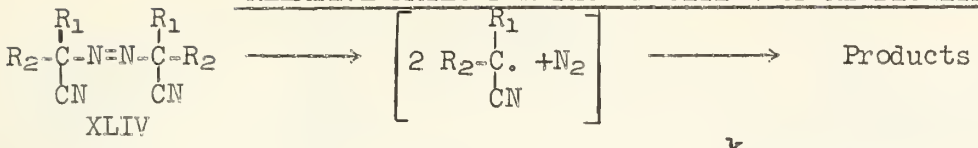
In the decomposition of azobisnitriles (XLIV) replacement of the various R groups with cyclopropyl groups leads to huge rate enhancements.[41-43]



XLII XLIII

TABLE 4

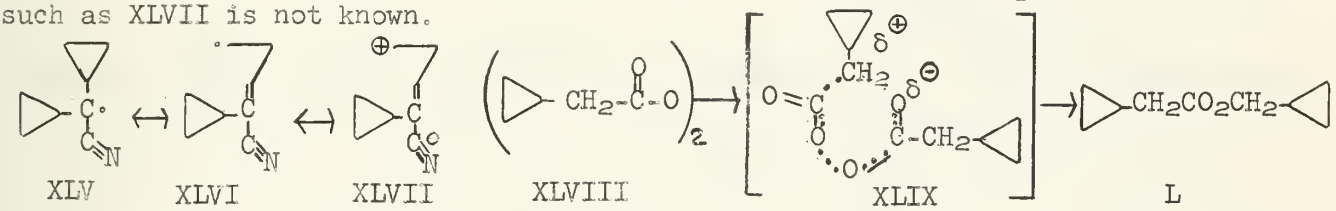
RELATIVE RATES FOR DECOMPOSITION OF AZOBISNITRILES[43]



XLIV

R_1	R_2	k_{rel} at 45°
CH_3	CH_3	1.0
cyclo-C_3H_5	CH_3	17.0
cyclo-C_3H_5	cyclo-C_3H_5	300.0

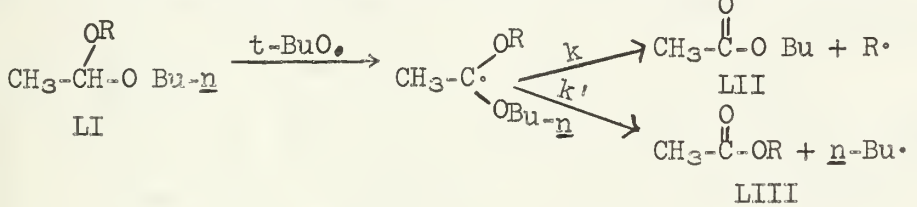
Since the rates are roughly additive, in a free energy sense, this enhancement can only be ascribed to some unusual conjugative ability of cyclopropane. Whether this enhancement is due entirely to stabilization of the radical XLV by some form of delocalization such as XLVI or due in part to some charge separated contribution such as XLVII is not known.



XLV XLVI XLVII XLVIII XLIX L

Hart[44,45] has found anomalous rates for the decomposition of cyclopropaneacetyl peroxide (XLVIII) compared to the rates of other cyclic acetyl peroxides. Since the major organic product, cyclopropylcarbinyl cyclopropaneacetate (L), was obtained in higher yield than the corresponding products for the decomposition of other cycloalkaneacetyl peroxides, it is not easy to determine the amount of free radical path envolved. A readily available non-free radical path (XLIX) can easily be imagined.

Studies on the decomposition of acetals[46] reveals that the cyclopropylcarbinyl radical is formed 3.89 times more readily than n-butyl radical. This result is arrived at by a comparison of the ratios of products LII:LIII, listed as k/k' in table 5. However, again a charge separated contribution can be imagined.



LI LII LIII

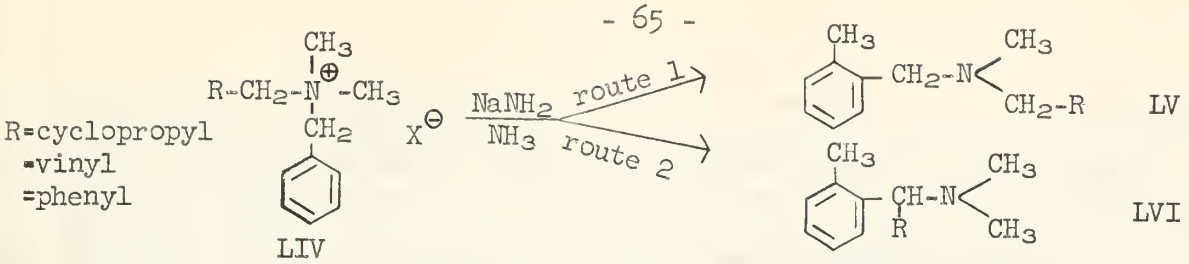
TABLE 5

RELATIVE RATES FOR DECOMPOSITION OF ACETALS

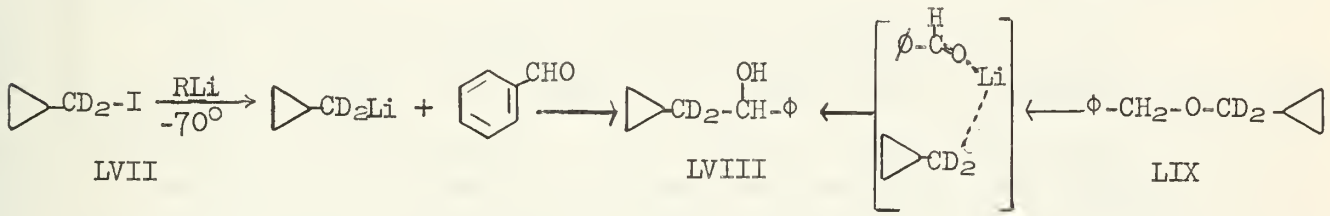
R	k/k'
n-Bu	1.0
cyclopropyl carbinyl	3.89
i-Pr	5.66
t-Bu	18.7
Benzyl	22.4

Several examples of cyclopropylcarbinyl anion have been reported and apparently it is not endowed with any unusually large amount of stability.

Bumgardner[47] believes that since route 2 is favored in the Sommelet-Hauser rearrangement of LIV, when R=cyclopropyl , the anion is stabilized by the cyclopropane ring. After statistical correction route 2 is favored over 1 by the ratio of 12:1. When R=vinyl or phenyl, route 2 is favored over route 1 to the extent that LV from route 1 is not formed. The implication here is that the intermediate anion formed is stabilized by the cyclopropane ring, however,certainly nowhere near to the extent that a phenyl or a vinyl group stabilizes.



Lansbury[49] has successfully prepared cyclopropylcarbinyl lithium and found that when the starting iodide (LVII) was labeled in the α position with deuterium, the product (LVIII), arising from reaction with benzaldehyde, had no scrambled deuterium. Furthermore, the fact that the rearrangement of benzyl cyclopropylcarbinyl-α,α -d_2-ether gives the same unrearranged product (LVIII) is believed to show that the anion has little, if any, "non-classical" character.



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MECHANISM OF THE BASE CATALYZED CLEAVAGE OF DISULFIDES

Reported by E. R. Lukenbach April 8, 1965

Introduction. - The subject of base catalyzed cleavage of disulfides has been of interest since the disulfide link was recognized as biologically important. As much research has made evident, disulfides are important in determining the tertiary structure of proteins, by crosslinking adjacent polypeptide chains or holding a chain in a loop. Much interest has developed recently in the specificity of enzymes as determined by their tertiary structure, as well as by features of their primary structure, in the "active site" concept.

Cleavage of disulfides occurs both in acid and in base, but very strong acid, greater than 1 N, is required for cleavage, while neutral water is sufficient for "basic" cleavage in some systems,[1,2] the rate of cleavage increasing rapidly with increasing pH.[3] Considering the mild conditions necessary, it is evident that the basic cleavage of disulfides may be a biologically important reaction. It is also of importance in the treatment of wool for weaving, in tanning, and in cosmetics, in the form of the "permanent wave."

The mechanisms which have been proposed for the basic cleavage of disulfides have been summarized in several papers.[4,5,6] It is the purpose of this seminar to review the evidence for these mechanisms, emphasizing recent contributions to the study of this problem.

Nucleophilic attack on sulfur.- The earliest mechanistic proposal, made by Schiller and Otto,[7] and widely used by Schoberl,[8] involves attack of the base on one of the sulfur atoms of the disulfide link, displacing a mercaptide ion:

$$R\text{-}S\text{-}S\text{-}R' + B^{\ominus} \longrightarrow R\text{-}S\text{-}B + {}^{\ominus}S\text{-}R'$$

As most of the early studies were done with hydroxide as base, a sulfenic acid, RSOH, was hypothesized as the first product of the reaction, along with the displaced mercaptide. Although only one such sulfenic acid, anthraquinone-1-sulfenic acid,[9] has been isolated, many of the products isolated from base cleavage of disulfides have been explained on the basis of further reactions of the sulfenic acids produced.

The first such reaction investigated was the cleavage of diphenyl disulfide[7,10] according to the equation:

$$2\ \ \phi\text{-}S\text{-}S\text{-}\phi \rightarrow 3\ \ \phi SH + \phi SO_2H$$

This was explained as a disproportionation of the sulfenic acid into the mercaptan and the sulfinic acid. Later studies[10] with various aromatic disulfides in base in the presence of benzyl chloride gave some benzaldehyde and benzoic acid, which were explained as the result of the oxidation of the benzyl chloride by the sulfenic acid.

Further studies by Schoberl[1,2,8,11,12,13] were conducted on α-carboxyl disulfides of the general type $\left[HO_2C\text{-}\overset{R}{\underset{R'}{C}}\text{-}S\right]_2$ where R and R' were various alkyl and aryl groups, as well as hydrogen. The presence of the carboxyl group and hydrogens on the α-carbon led to a new reaction, loss of hydrogen sulfide from the sulfenic acid to leave the carbonyl group. For instance,[11] from αα'-diphenyl dithiodiglycolic acid, I, were obtained α-phenyl thioglycolic acid, II, in 50% yield, and α-phenyl glyoxylic acid, III, in 45% yield:

$$\underset{\text{I}}{\left[HO_2C\text{-}\overset{\phi}{\underset{H}{C}}\text{-}S\right]_2} \xrightarrow{OH^{\ominus}} \underset{\text{II}}{HO_2C\text{-}\overset{\phi}{\underset{H}{C}}\text{-}S\text{-}H} + \underset{\text{III}}{\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2H}$$

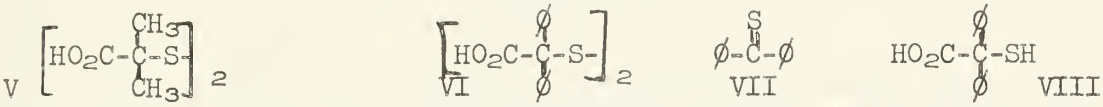
III should have been expected in 50% yield if it came from the sulfenic acid. Hydrogen sulfide was present in the solution, but it was not isolated quantitatively. In those reactions which were studied kinetically,[2] no correlation was found between the production of hydrogen sulfide and mercaptan groups, indicating that the production of hydrogen sulfide occurs by a secondary process. However, on completion of the reaction, approximately equal amounts of mercaptan and hydrogen sulfide were found.

In the case of dithio-diglycolic acid, IV, only thioglycolic acid (60%) and oxalic acid (10%) were obtained. The fact that the excess of the thioglycolic acid over theoretical was the same as the yield of oxalic acid indicates that the hypothesized sul-

$$\underset{\text{IV}}{\left[HO_2C\text{-}CH_2\text{-}S\right]_2}$$

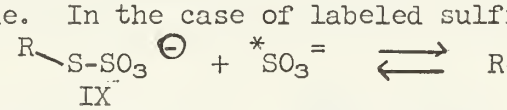
fenic acid had oxidized the expected glyoxylic acid, producing equal amounts of the acid and the mercaptan.

In investigation with a more substituted dithiodiglycolic acid,[13] it was found that the di-(α-dimethyl glycolic) disulfide, V, did not react at all on heating in 5 N sodium



hydroxide. However, treatment of di(α-diphenyl glycolic) disulfide, VI, under the same conditions produced a blue oil, which was characterized as the diphenyl thioketone, VII, plus α-diphenyl thioglycolic acid, VIII. VII was theorized to have arisen from the sulfenic acid by simultaneous loss of carbon dioxide and water. The fact that the di(α-dimethyl glycolic) disulfide was unreactive was attributed to a steric "crowding" effect, which prevents base attack on the sulfur atoms. The activating effect of the phenyl groups, compared to the methyl groups, allowed a certain degree of reactivity in the di(α-diphenyl glycolic) disulfide.

Later investigation by Fava and Iliceto[14,15] of the steric effects of substituent groups on a disulfide showed that the basic cleavage of disulfides is first order in base and first order in disulfide. In the case of labeled sulfite exchange in alkyl thiosulfates (Bunte salts), IX,



IX

the order of reactivity was:

substituent R	relative rate
methyl	1
ethyl	.5
isopropyl	7×10^{-3}
tertiary butyl	6×10^{-6}

According to these kinetics and the known geometry, X,[16,17] a backside attack was hypothesized:

X

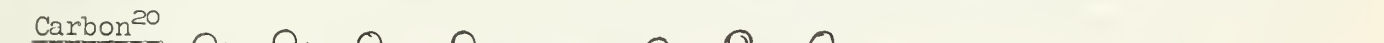
(A)

This hypothesis has been confirmed in the case of radical reactions of disulfides by Pryor and Pickering.[18]

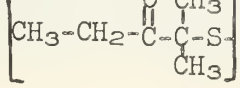
Later studies by Schoberl and Ludwig[19] indicated that sulfite and cyanide would cleave cystine. Parker and Kharasch[4] continued the studies with other bases, and established an order of relative nucleophilicity in attack on sulfur. It was found that sulfur and carbon nucleophilicities were not necessarily parallel. This was thought to be due to the fact that sulfur can use its 3d orbitals to form transitory bonding in the transition state, and so atoms with more polarizable electrons, such as phosphorus, sulfur, and arsenic, will react more readily than oxygen or nitrogen.

Sulfur[4] Order of Nucleophilicity

Carbon[20]



Recent studies have used this mechanism with equal success in explanation of observed results. Asinger, et.al.,[21] in studies on αα'-diketo disulfides, found that mercaptans and diketones were the usual products in hydroxide cleavage. The diketone is again explained as the product of the loss of hydrogen sulfide from the keto sulfenic acid. Cleavage by cyanide gave the sulfide and thiocyanate salt. This was explained by the attack of the mercaptide on the thiocyanate with displacement of thiocyanate ion. Attack of hydroxide on the tertiary αα'-diketo disulfides, such as 4,4,7,7 tetramethyl-3,8-diketo-5,6-dithia-decane, XII, produced the mercaptan and the sulfinate,

XII 

which is again explained by disproportionation of the intermediate sulfenate to the sulfinate and the mercaptan.

Studies by Parker and Kharasch[22] on the products of base cleavage of unsymmetrical disulfides, both with and without trapping agents, have led them to the conclusion that the sulfur bonded to the more electrophilic group will be displaced as the mercaptide. The sulfur next to the more electrophilic group would have a lower electron density and so be a better site for nucleophilic attack than the sulfur next to the less electrophilic group. However, the more electrophilic group would be more able to stabilize the growing negative charge on the adjacent sulfur in the transition state if this group were displaced as mercaptide. Thus it appeared that the reaction was more dependent on the stability of the leaving group than on the ease of bonding with the attacking group.

Heterolytic equilibrium. After further work, Schoberl and Wagner[23] proposed that the same results as were explained by a sulfenic acid intermediate could be explained by the equilibration of the disulfide to positive and negative-charged species:

$$R\text{-}S\text{-}S\text{-}R' \rightleftharpoons R'\text{-}S^{\ominus} + RS^{\oplus}$$

The observed products were due to the further reactions of the $RS^{\oplus}$ species, by loss of a proton (B), loss of elemental sulfur (C), direct reaction with base (D), and also reaction with hydroxide to give the sulfenic acid, which could then react further (E).

$$R\text{-}\underset{R'}{\overset{H}{C}}\text{-}S^{\oplus} \longrightarrow R\text{-}\underset{R'}{C}{=}S + H^{\oplus} \xrightarrow{H_2O} R\text{-}\underset{R'}{C}{=}O \qquad (B)$$

$$R\text{-}S^{\oplus} \longrightarrow R^{\oplus} + S^{\circ} \qquad (C)$$

$$R\text{-}\underset{X}{C}\text{-}S^{\oplus} \xrightarrow{B^{\ominus}} R\text{-}\underset{X}{C}\text{-}B + S^{\circ} \qquad (D)$$

$$R\text{-}S^{\oplus} \xrightarrow{OH^{\ominus}} RSOH \qquad (E)$$

The suggestion of the heterolytic cleavage mechanism was not well received, and Foss[24] has presented evidence against it. First, by analogy, he points out that the disulfide bond is stronger than the peroxide bond by approximately 20 kcal/mole. Since many other reactions of the disulfide group are similar but reflecting this extra bond strength, the factor leading to easier base cleavage must be the ability of sulfur to use its 3d orbitals to form transitory bonds in the transition state, aiding nucleophilic attack. More concrete evidence against this mechanism is the fact noted by Foss that all reactions studied kinetically have been found to be second order, so some sort of Sn2-like reaction must be favored over the Sn1-like reaction suggested by Schoberl and Wagner.

Beta elimination. It was observed by Clark and Inouye[25] that the sodium hydroxide cleavage of cystine in the presence of plumbite gave 75-80% lead sulfide and 20-25% sodium thiosulfate. This was explained as due to elimination of sodium disulfide from the cystine, followed by reaction with the plumbite:

$$4\ Na_2S_2 + 6\ Pb(OH)ONa + 3\ H_2O \longrightarrow 6\ PbS + Na_2S_2O_3 + 12\ NaOH$$

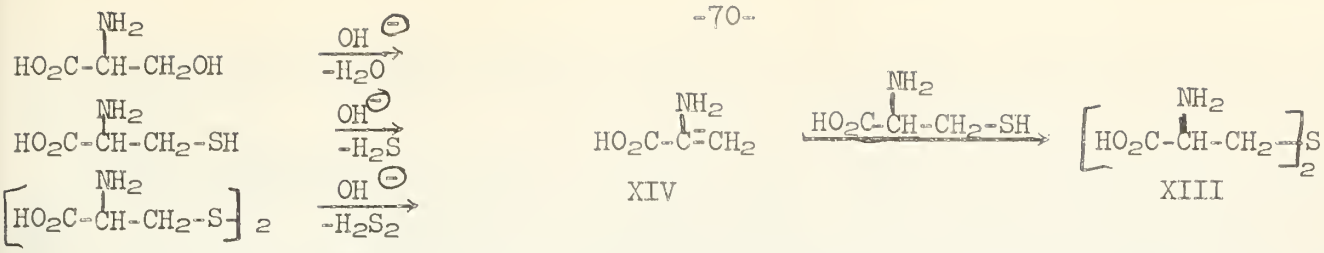
No mechanism for the elimination of the sodium disulfide was proposed.

Nicolet,[26] in work on cysteine and derivatives proposed a mechanism for the elimination of hydrogen sulfide. It was proposed that enolization of the carboxyl carbonyl could be followed by elimination of hydrogen sulfide as well as return to keto form:

$$HS\text{-}CH_2\text{-}\underset{NH_2}{CH}\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH \rightleftharpoons HS\text{-}CH_2\text{-}\underset{NH_2}{\overset{OH}{C}}{=}C\text{-}OH \rightleftharpoons CH_2{=}\underset{NH_2}{C}\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH$$

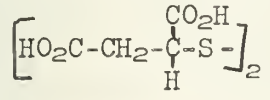
It was also proposed that a similar mechanism could operate in cystine, with a double elimination leading to production of hydrogen disulfide or its salt.

It was soon discovered that a new substance, called lanthionine, 2,6-diamino-4-thiapimelic acid, XIII,[27] could be isolated from hydrolysates of proteins. Nicolet and Shinn[28] were able to isolate lanthionine from a base hydrolysis of silk in the presence of added cysteine. This supported the concept of elimination to yield the α-amino acrylic acid, XIV. Also Swan[29] isolated lanthionine from hydrolysis of cystine derivatives:



Tarbell and Harnisch[30] were the first to formulate the elimination to give the unsaturated product as an attack on a hydrogen beta to the sulfur, leading to the beta-elimination type of mechanism. As evidence they quoted the fact that carbonyl groups next to the beta carbon atom led to highly increased reaction rates. In addition, a masked carboxyl group activated much more than a free carboxyl group. Since in these hydrolyses the free carboxyl would be in the salt form, carrying a negative charge, the attack of a negatively charged base alpha to this group would be expected to be inhibited.

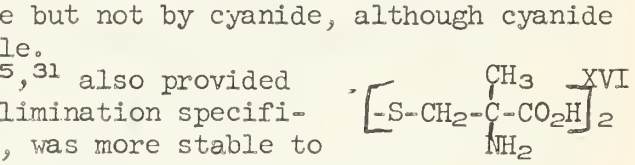
As evidence for the need for the elimination reaction in addition to the nucleophilic attack on sulfur, it was noted by Parker and Kharasch[4] that succinic disulfide, XV



XV

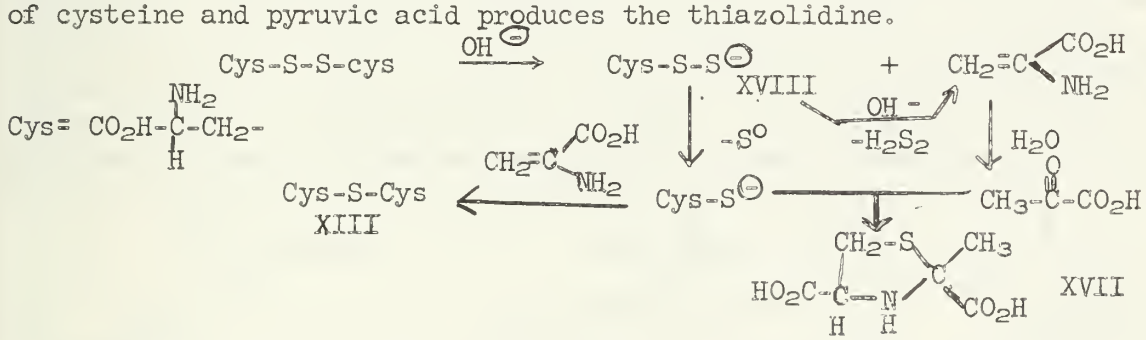
was cleaved by hydroxide but not by cyanide, although cyanide is a stronger nucleophile.

Stapleton and Swan[5,31] also provided evidence for the beta elimination specifically by noting that $\alpha\alpha'$-dimethyl cystine, XVI, was more stable to base attack than cystine. If only nucleophilic attack on sulfur or attack on hydrogens alpha to sulfur were mechanisms operating in this system, then the reaction rate should be about the same in cystine and $\alpha\alpha'$-dimethyl cystine. The fact that the $\alpha\alpha'$-dimethyl cystine does react, although about one twentieth as fast as cystine, indicates that other mechanisms also are operating.

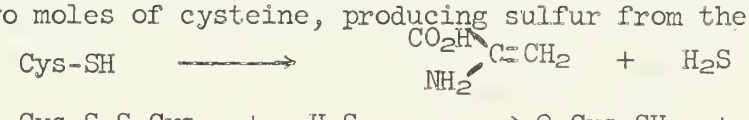


XVI

Dann, Oliver, and Gates[32] modified the decomposition scheme for disulfides, after noting that hydrogen disulfide decomposed to hydrogen sulfide and sulfur. They also had to explain the production, which they observed, of 2-methyl thiazolidine-2,4-dicarboxylic acid, XVII, from the hydroxide cleavage of cystine. They proposed that on elimination from one side of the cystine molecule, α-amino acrylic acid, XIV, and cysteine disulfide, XVIII, are produced. The cysteine disulfide may then undergo beta elimination, producing hydrogen disulfide, which will decompose to hydrogen sulfide and sulfur, or the cysteine disulfide may itself lose sulfur, producing cysteine, which can react with the α-amino acrylic acid to produce lanthionine, XIII. Further studies disclosed that one product of the cleavage of cystine was pyruvic acid. This was proposed to be due to the hydrolysis of the α-amino acrylic acid. The reaction of cysteine and pyruvic acid produces the thiazolidine.



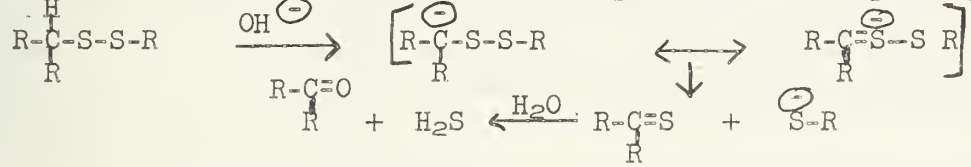
Elliott, Asquith and Hobson[33] suggested another possible variation on the beta elimination theme, when they observed that cysteine is necessary for cleavage of cystine by refluxing ethylamine. It was hypothesized that the cysteine underwent a beta elimination, yielding hydrogen sulfide, which then would serve as a reducing agent, cleaving the cystine to two moles of cysteine, producing sulfur from the hydrogen sulfide:



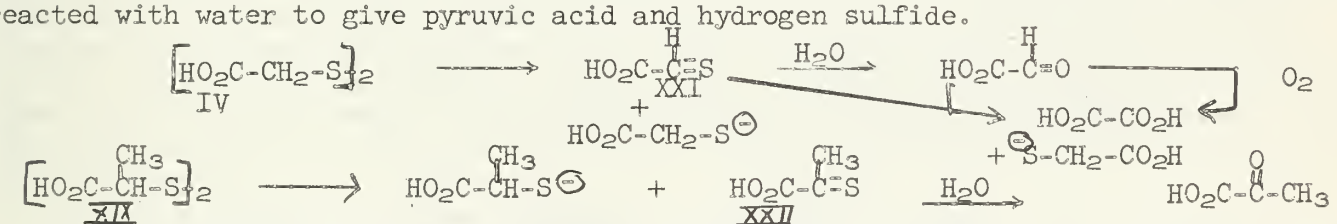
Wallace, Hofman, and Schriesheim[34] have recently demonstrated the beta elimination reaction in systems not activated by carbonyl groups, by the use of tertiary butoxide in dimethyl sulfoxide on n-butyl- and t-butyl-disulfides. After prolonged heating at 55° C,

n-butyl disulfide gave 1-butene, cis-2-butene, and trans-2-butene in a 1:3:6 ratio in a total 30% yield. Under similar conditions t-butyl disulfide gave an 85% yield of isobutylene.

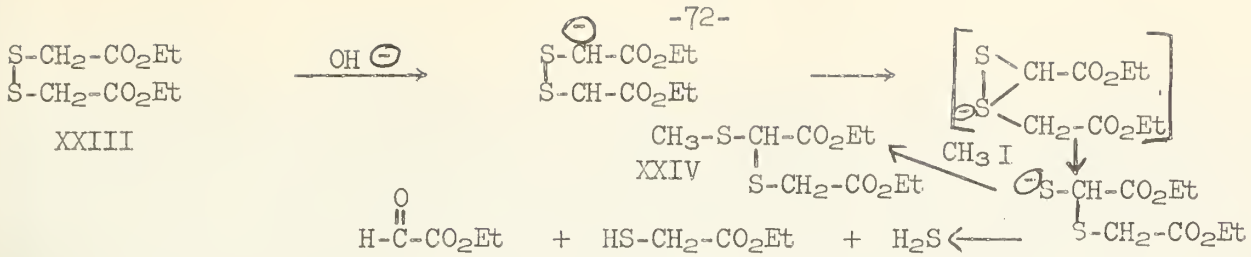
Alpha elimination. Rosenthal and Oster[35,36,37] noted, as did Parker and Kharasch[4], that agents such as azide, cyanate, and acetate do not cleave disulfide, although they are of comparable nucleophilicity with hydroxide. Thus, they also hypothesized that a proton abstraction would better explain the cleavage reaction with hydroxide. However, they conducted ultraviolet absorption studies on disulfides in base. The disulfides generally have a non-specific absorption at low pH values, but on addition of base, the absorption changes to a specific pattern, depending on the substitution of the disulfide group. This shift occurred only for disulfides having hydrogens on the carbon next to the sulfur. They proposed that this was due to the abstraction of the proton alpha to the sulfur. This produces a negative charge on carbon, which may resonate with a form carrying the charge on sulfur, with a carbon-sulfur double bond. The carbon-sulfur double bond was suggested as the chromophore. This resonance hybrid would have a center bond weakened by the negative charge on the sulfur. This intermediate could decompose to give a thioketone and a mercaptide. The thioketone would react with water in most cases to give the ketone plus hydrogen sulfide.



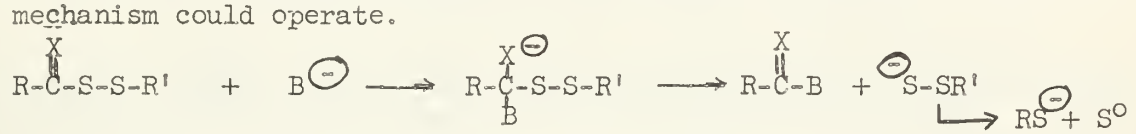
Danehy and Kreuz[38,39] studied a series of alpha and beta carboxyl disulfides, subjecting them to hydroxide cleavage and analyzing for the products, in a manner similar to the studies by Schoberl.[1,2] In studying dithiodiglycolic acid, IV, they isolated thioglycolic and oxalic acids, along with hydrogen sulfide, as products. With $\alpha\alpha'$-dimethyl dithiodiglycolic acid, XIX, α-methyl thioglycolic acid and pyruvic acid, along with hydrogen sulfide, were obtained, although with a reaction rate one twenty-fifth that of the unsubstituted disulfide. 4,5-dithia-suberic acid, XX, was also cleaved, but at a very much slower rate, and the products accounted in mercaptan groups for all of the sulfur present in the reagents. This may have been due to a mechanism similar to that described by Elliott, Asquith and Hobson.[33] The reactions of the alpha carboxyl disulfides were explained by an alpha elimination mechanism, giving the thiocarbonyl groups, which reacted with base to give the carbonyl groups. The glyoxylic acid produced from dithio diglycolic acid, IV, could then react further by oxidation by the thiocarbonyl-glyoxylic acid, XXI, giving oxalic acid and thioglycolic acid. In fact only a 50% excess of mercaptan to hydrogen sulfide was observed, instead of the 3:1 ratio expected from this mechanism. Air oxidation of the glyoxylic acid to oxalic acid is a possible explanation of this fact. In the case of the $\alpha\alpha'$-dimethyl dithiadiglycolic acid, XIX, a 1:1 ratio of mercaptan to hydrogen sulfide was observed, indication that all of the thiocarbonyl pyruvic acid, XXII, produced, reacted with water to give pyruvic acid and hydrogen sulfide.



Attack on Alpha Hydrogen Followed by Rearrangement. Howard,[40] in studies on diethyl dithia diglycolate, XXIII, succeeded in isolating, on addition of methyl iodide, the methyl mercaptal, XXIV, of thiocarbonyl ethyl glyoxylate and ethyl thioglycolate. On the strength of this observation he proposed a detail modification of the alpha elimination mechanism. He proposed that after elimination of the alpha hydrogen, the carbanion attacks the beta sulfur, which yields an intermediate which could reopen to give the hemimercaptal, which would then be cleaved by water to give the observed carbonyl and mercaptan products.



Attack on Unsaturated Carbon. Fromm[41,42] proposed that in the case where the alpha carbon of a disulfide was double bonded to oxygen, nitrogen, sulfur, or phosphorus, the base would attack at the unsaturated carbon, displacing the monosubstituted hydrogen disulfide, which would decompose to the mercaptan plus sulfur. This mechanism has received little further attention, because of the lack of substrates of the type in which this mechanism could operate.

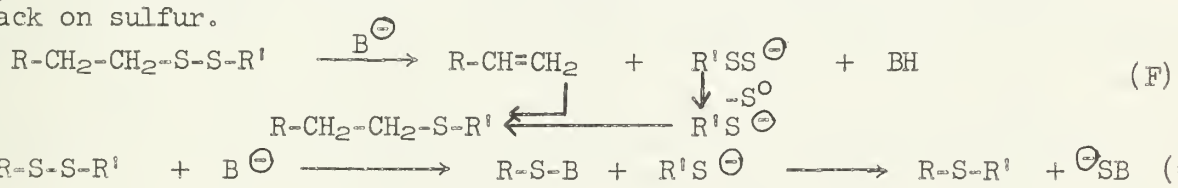


Cyanide Cleavage of Unsymmetrical Disulfides. Hiskey and Carroll[43] criticized the earlier work of Parker and Kharasch[22] in their studies of cyanide cleavage of disulfides, in that the product analysis was incomplete, in most cases being only an identification of the mercaptan produced in major yield. In addition, the disulfides tested in this work had at least one aromatic substituent. In no case was a purely aliphatic disulfide tested.

Hiskey and Carroll noted that the cleavage of disulfides must be reversible, as indicated by the fact that symmetrical disulfides will cleave, but only in the presence of a reagent which will draw the reaction to completion, such as a mercaptide scavenger. Starting from this basis, they proceeded to cleave various unsymmetrical disulfides, with complete product analyses, in order to relate the direction of cleavage with the pKa's of the component mercaptans.

The studies were first carried out using methanol as solvent, as had been done in previous studies, but many of the expected products were not found, due to reaction with the solvent. When acetonitrile was used, the reactions became easier to study. As a result of a series of cleavages, correlated with the difference of pKa's of the component mercaptans, it was discovered that if the ΔpKa was greater than 1.80, the cleavage was unidirectional. In the ΔpKa range of 1.63 to 1.05, a measure of attack on both sulfur atoms occurred. With a ΔpKa less than 1.05, the disulfide was quite inert, with no cleavage at all occurring with ΔpKa of zero, that is, in a symmetrical disulfide.

In further work[44] on disulfides with a ΔpKa of intermediate range, allowing cyanide attack on either sulfur, Hiskey and Carroll observed the formation of the corresponding monosulfides, even in the presence of what had been considered highly efficient mercaptide scavengers. This sulfide was observed only when the thiocyanate produced had a labilized alpha carbon atom or when a highly nucleophilic mercaptide was formed. The similarity of this sulfide formation to the formation of lanthionine from cystine prompted additional investigation. Two alternate mechanisms were proposed. First, (F), a beta elimination could yield an olefin and a disulfide, which would lose sulfur to form the mercaptide, which would recombine with the olefin to form the sulfide. Second, (G), the mercaptide produced could attack directly the product produced by the base attack on sulfur.

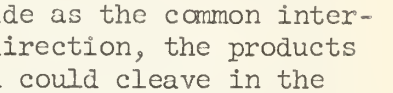


It was considered that the second mechanism was the more likely, from the observations stated above, requiring a labilized alpha carbon atom or strong nucleophile to produce the sulfide. Also, while hydroxide might give the proton abstraction, cyanide and other bases studied are not strong enough bases to do this. The products of this type of reaction have been isolated by other researchers, for example, thiocyanate from cyanide cleavage.[21]

In studying the efficiency of the trapping agents, a pair of reactions were run, with the complementary thiocyanates and mercaptides in the presence of the scavenger. In both cases the same products were obtained, indicating that the reagents were able to equilibrate to give the more stable mercaptide before the "trapping agent" was effective. It was proposed that the observed results could be explained either by rapid cleavage and recombination in both directions, with the disulfide as the common intermediate, or the cleavage of the disulfide in one or the other direction, the products of which could combine rapidly to form a new intermediate which could cleave in the opposite direction to give the opposite products. XXV was proposed as a possible such intermediate.

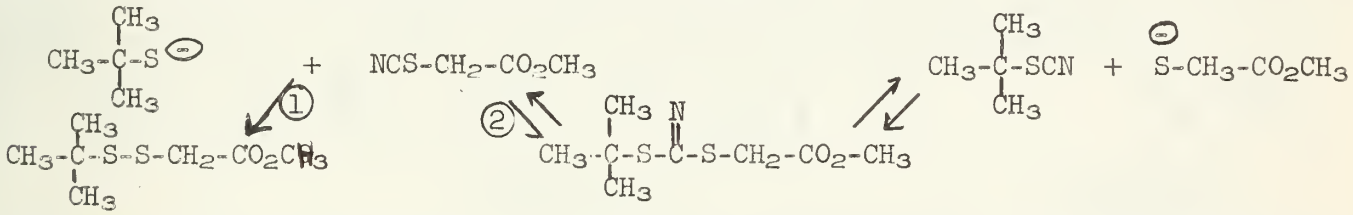
$$RS^{\ominus} + R'\text{-}S\text{-}C{\equiv}N \rightleftharpoons \underset{\text{XXV}}{R\text{-}S\text{-}\overset{\overset{N}{\|}}{C}\text{-}S\text{-}R'} \rightleftharpoons R\text{-}S\text{-}C{\equiv}N + R'\text{-}S^{\ominus}$$

In order to distinguish between the two above possibilities,[45] methyl-5,5-dimethyl-3,4-dithia-hexanoate, XXVI, was studied. This disulfide is unreactive to cyanide under the usual conditions due presumably to the steric effect of the t-butyl group.



XXVI

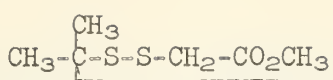
Thus, if t-butyl mercaptide and methyl-α-thiocyanato-acetate are mixed, and the disulfide is the intermediate of exchange, then in this case the disulfide should be isolated, since it does not cleave in either direction. On the other hand, if an intermediate similar to XXV is present, some t-butyl thiocyanate and methyl thioglycolate should be formed.



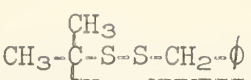
Experimentally, the disulfide is isolated, indicating that it is the intermediate in the equilibration of the possible products. From this it is apparent that one cannot tell where the initial attack by base occurs in disulfides, according to the data of previous research, but the products observed were those governed by thermodynamic, not kinetic factors.

In attempting to determine the initial site of cyanide attack, the fact that the symmetrical monosulfide corresponding to the less basic mercaptide was produced in the presence of trapping agents was considered to indicate that base attack was initially on the more positively charged sulfur atom, yielding the more basic mercaptide, which equilibrates to yield the less basic mercaptide and the thiocyanate corresponding to the more basic mercaptide, which would be the more stable products. The initially produced thiocyanate, corresponding to the less basic mercaptide, and the less basic mercaptide itself, produced through equilibration, can react to form the sulfide with displacement of thiocyanate. If attack were on the more negatively charged sulfur, the more stable products would be produced initially, and the mercaptide would be trapped before sufficient equilibration could occur to give the corresponding thiocyanate in significant yield. This evidence for attack on the more positive sulfur atom is in contradiction to the conclusions of previous researchers.[22]

In order to test the concept of initial displacement of the less stable mercaptide, the use of a t-butyl group as the less electrophilic substituent on a disulfide would serve to show cleavage by attack on the farther, more positive sulfur atom occurs, as any cleavage would be expected to come from this attack. With previous scavengers, cleavage of t-butyl substituted disulfides has not been detected. However, since the equilibration is faster than previous scavenging reactions, it appears that thiocyanates should serve as good scavengers. When benzyl thiocyanate is used as a scavenger for cyanide cleavage of t-butyl methyl acetate disulfide, XXVII, t-butyl benzyl disulfide, XXVIII, is isolated, indicating that t-butyl mercaptide was produced. This shows that base attack may have occurred on the more positive sulfur atom.



XXVII

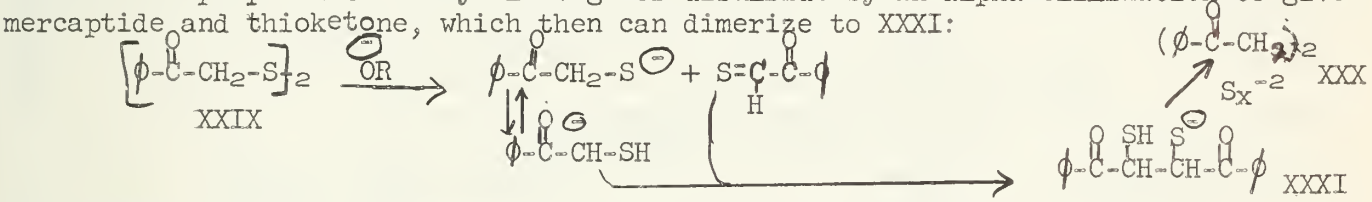


XXVIII

In addition to the attack of t-butyl mercaptide on benzyl thiocyanate, t-butyl benzyl disulfide could be produced from reaction of benzyl mercaptide and t-butyl thiocyanate or attack of benzyl mercaptide on the original disulfide. The first alternative is eliminated by mixing benzyl thiocyanate, t-butyl thiocyanate and methyl thioglycolate mercaptide, and observing that the products obtained are different from those of the original reaction. Thus, equilibration is not occurring in the presence of benzyl thiocyanate. If benzyl- or methyl thioglycolate-mercaptide attacked the disulfide to give the t-butyl mercaptide, one should be able to isolate the new disulfide produced, but none is observed. The presence of benzyl mercaptide should be indicated by the presence of dibenzyl sulfide. This is not observed in the original reaction. Thus, the alternative possibilities are apparently not occurring and attack does occur at the more positive sulfur atom. This cannot be generalized to other systems, because of the t-butyl group emphasizing the reaction on the one sulfur atom. However, the idea of rapid equilibration from initial attack on the more positive sulfur to yield finally the more stable products appears applicable to all systems.

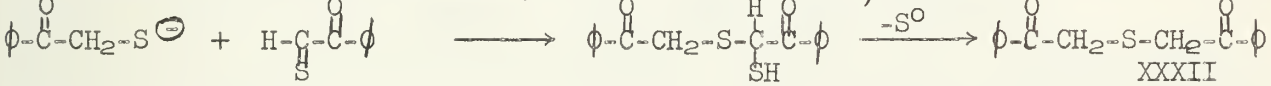
Alkoxide Cleavage of Disulfides. Although the subject of strong base cleavage of disulfides has been fairly thoroughly explored, the cleavage of phenacyl disulfide, XXIX, has previously defied explanation. Hiskey and coworkers undertook to analyze this reaction.[6,46] The products isolated were XXX, XXXI, XXXII, and XXXIII.

It was discovered[47] that the monobasic salt, XXXI, could be reduced by polysulfide to give XXX. Thus, this appears to be one of the intermediate reactions. The formation of XXXI was proposed to be by cleavage of disulfide by an alpha elimination to give mercaptide and thioketone, which then can dimerize to XXXI:



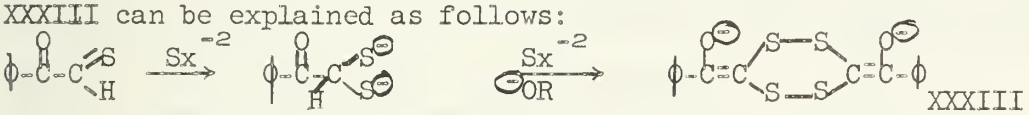
XXIX XXX XXXI

A different recombination could yield the monosulfide, XXXII:



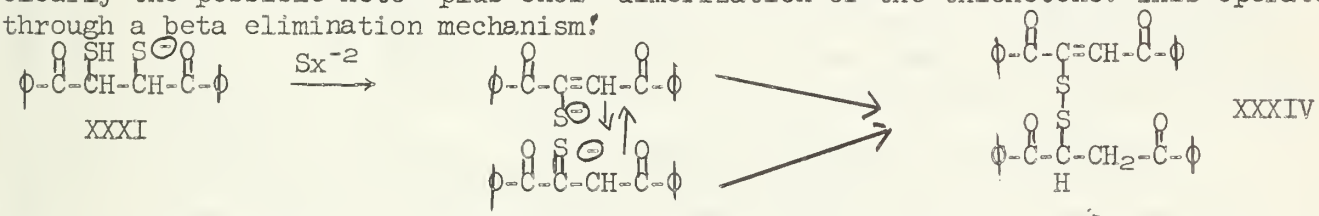
XXXII

XXXIII can be explained as follows:



XXXIII

A further component, XXXIV, of the system isolated from subsequent tests shows more clearly the possible keto- plus enol- dimerization of the thioketone. This operates through a beta elimination mechanism:



XXXI XXXIV

Although analagous reactions support these reaction schemes, there is a lack of direct evidence for some of the proposed reaction intermediates, and some products are unexplained, which leaves the reaction still poorly defined. Further work by this group may serve to better clarify the system, and the conditions under which one or another reaction might be favored.

Conclusion. The mechanisms proposed by various groups all have factual backing. However, certain necessary features are required in the disulfide molecule to favor one mechanism over another. In general, if there are no ionizable protons, or if the base is a weaker base than it is a nucleophile, the attack will be on sulfur. The protons which are most activated are the ones which will be ionized, and so will determine whether alpha or beta elimination occurs. In complex systems, it is still difficult to predict which scheme will be favored. The fact that symmetrical disulfides are cleaved by strong bases but not by strongly nucleophilic weak bases indicates a

different type of intermediate is produced which can react further, thereby forcing the initial reaction to completion. This type of reaction must be considered in a different light from the nucleophilic attack mechanism.

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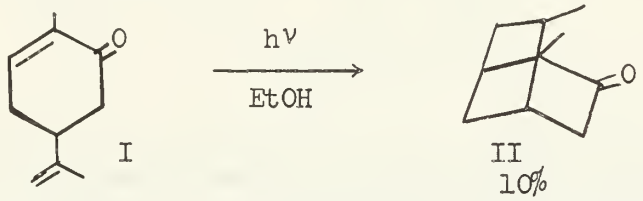
PHOTOCYCLOADDITIONS OF UNSATURATED CARBONYL COMPOUNDS

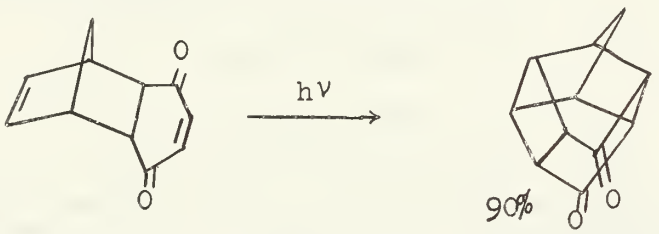
Reported by D. S. Hetzel April 12, 1965

Introduction. - Recent photochemical studies with α,β unsaturated ketones have led to the discovery of some interesting and unusual transformations.[1] One of these transformations, photocycloaddition with unactivated olefins, has attracted considerable attention. This seminar will review the synthetic scope of this versatile reaction and present some current mechanistic hypotheses. The long known photodimerization of unsaturated ketones and the intramolecular photocycloaddition of isolated ethylenic bonds will, in general, not be considered here. A review of early work is available.[2]

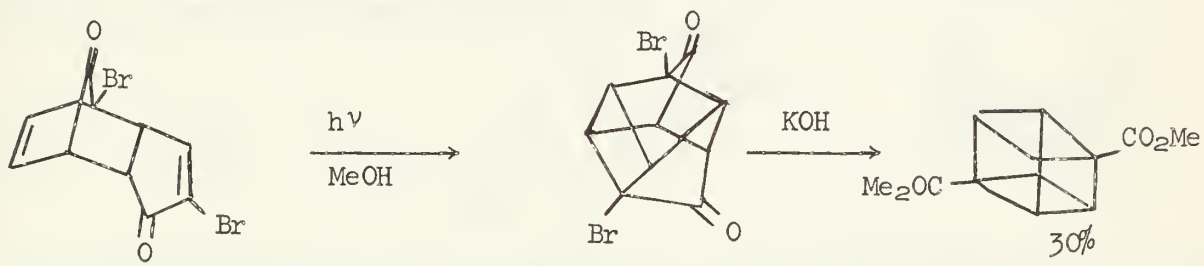
Photocycloadditions of Alicyclic Unsaturated Ketones. - In 1908, Ciamician and Silber observed that carvone (I) was converted to a saturated isomer by exposure to Italian sunlight for one year.[3] The photoisomer was designated carvonecamphor and assigned structure II. Buchi and Goldman confirmed this assignment in their reinvestigation of the reaction in 1957.[4]



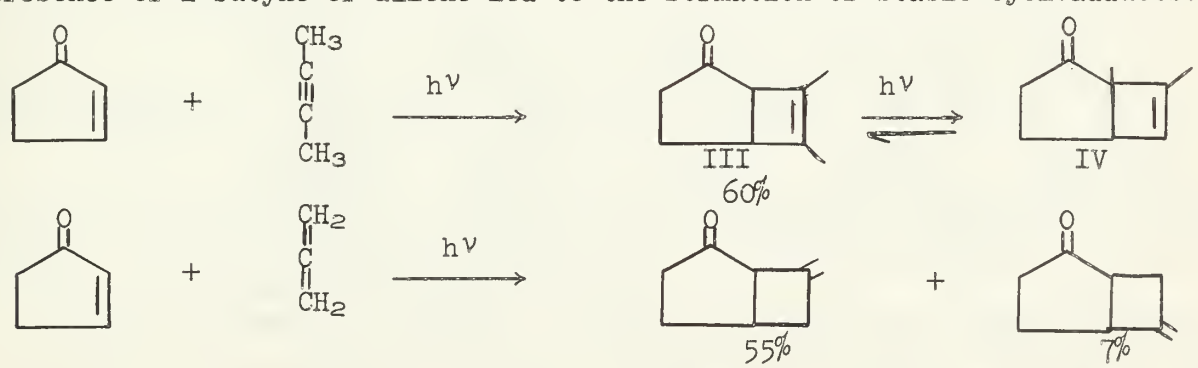
Similar intramolecular photocycloadditions have been noted with cyclohexadiene and cyclopentadiene - benzoquinone Diels-Alder adducts.[5]



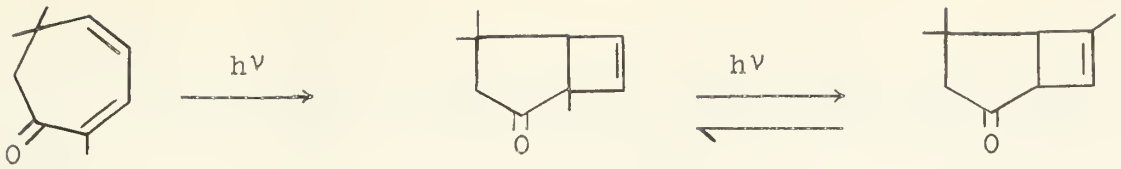
A reaction of this type was also a critical step in Eaton's cubane synthesis.[6]



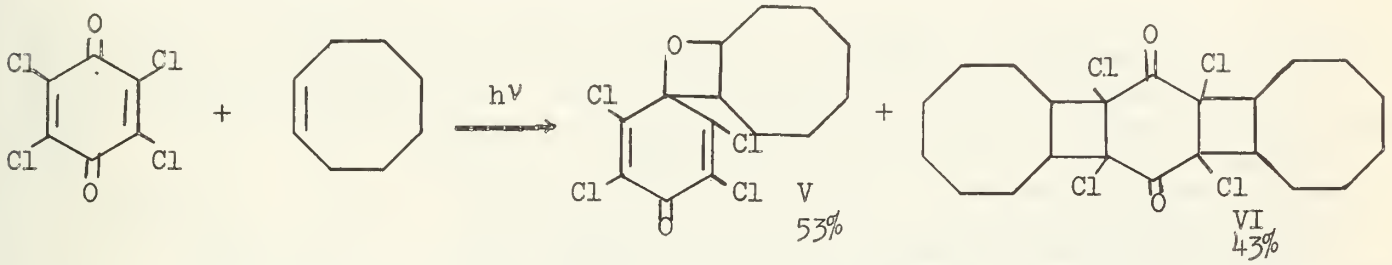
Recent workers have also observed intermolecular photocycloadditions with a wide variety of substrates. Eaton showed that irradiation of 2-cyclopentenone in the presence of 2-butyne or allene led to the formation of stable cycloadducts.[7]



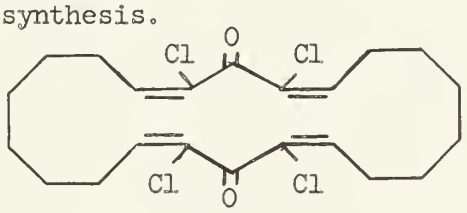
The photo-equilibrium established with the butyne adduct (III-IV) is analogous to the equilibration noted by Buchi and Burgess in the photolysis of eucarvone.[8]



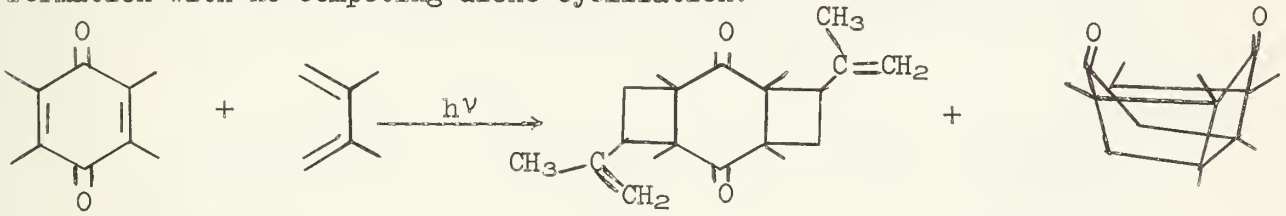
Irradiation of chloranil in excess cyclooctene is reported to yield both 1:1 and 1:2 adducts.[9] The 1:1 adduct showed infrared absorption characteristic of a conjugated carbonyl, had an ultraviolet λ max at 262 mμ and yielded a monohydric phenol upon hydrogenation (1.0 equivalents). Consequently it was assigned the oxetane structure V. Oxetane formation is often observed when aromatic or saturated ketones are photolyzed in the presence of olefins.[10]



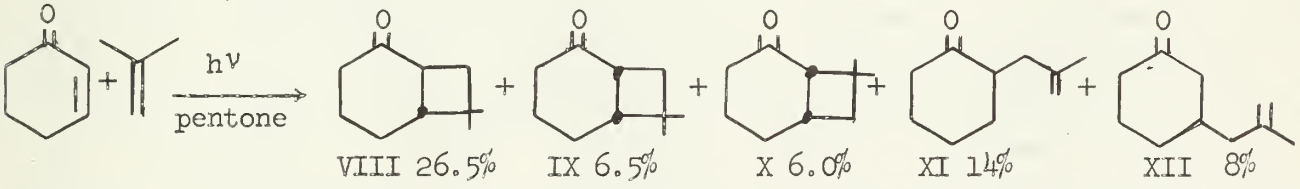
The 1:2 adduct had infrared absorption typical of an unconjugated carbonyl, a λ max of 295 mμ and a parent peak in the mass spectrum at m/e = 466. It was assigned the pentacyclic structure VI. In refluxing tetralin, this cycloadduct underwent ring opening to the unsaturated macrocycle VII. Extending this reaction may establish a convenient macrocycle synthesis.



Schenck found that photolysis of duroquinone in the presence of 1,3 dienes yields not only pentacyclic 1:2 adducts, but also cagelike 1:1 cycloadducts.[11] Irradiation with light of wavelength greater than 416 mμ led exclusively to adduct formation with no competing diene cyclization.[12]



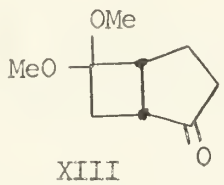
The photocycloadditions of 2-cyclohexenone have been studied by Corey.[13] Adduct formation occurred with isobutylene, butene, allene, cyclopentene, 1,1-dimethoxy ethylene, vinyl acetate and methyl vinyl ether. A quantitative product analysis was done on the isobutylene reaction.



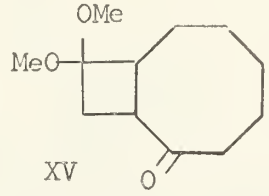
Of interest here are the great dominance of the 7,7-dimethyl bicyclo(4.2.0)octanone-2 (VIII+IX) over the 8,8-dimethyl isomer (X) and the favored production of the thermodynamically less stable trans isomer (VIII).

An attempt was made to determine the effect of ring size on product composition and stereochemistry. Cyclopentenone and 1,1-dimethoxy ethylene (chosen for its high reactivity and ease of product identification) photolyzed under the standard conditions gave the expected photocycloadduct, 6,6-dimethoxy bicyclo(3.2.0)heptanone-2 (XIII), in 60% yield. Cyclohexenone, as indicated, formed a cycloadduct, isolated

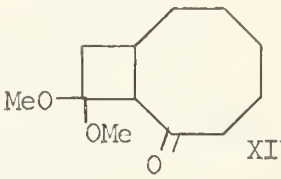
in 70% yield. 2-cycloheptenone failed to form a photoadduct with dimethoxy ethylene. No explanation was advanced for this observation. Cis-2-cyclooctenone did yield an adduct (37% yield) which was identified as 10,10-dimethoxy bicyclo(6.2.0) decanone-2 (XIV). This structure was unexpected since the 9,9-dimethoxy compound (XV) would be predicted on the basis of the products obtained with cyclopentenone and cyclohexenone.



XIII

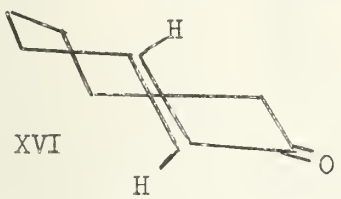


XV



XIV

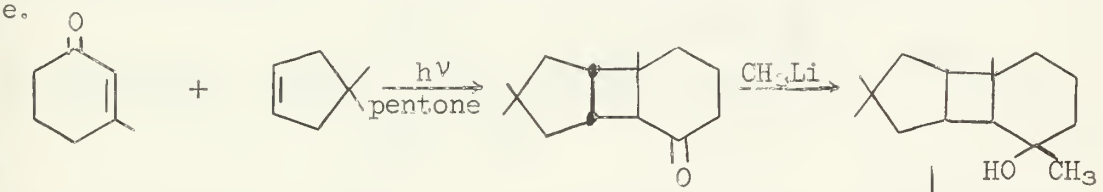
It was found, however, that a photoisomerization of cis-cyclooctenone to a very reactive trans-cyclooctenone (XVI) occurred prior to addition. Cycloaddition was then thermal rather than photolytic. Eaton independently studied this phenomenon and found that about 80% conversion to a product having u.v. (λmax = 283mμ) and infrared (5.79 μ) absorptions characteristic of an unconjugated ketone could be realized.[14] The nmr spectrum indicated two vinyl protons. This highly strained structure reacts vigorously with 1,1-dimethoxy tetrachloro cyclopentadiene at room temperature whereas cis- cyclooctenone reacts only sluggishly at 90°.



XVI

The effect of methyl substitutents on cyclohexenone was also examined. 3-methyl, 2-cyclohexenone added normally to isobutylene to give a product mixture very similar to that obtained with unsubstituted cyclohexenone. A 2-methyl substitutent, however, greatly diminished reaction rate and led to a very complex mixture.

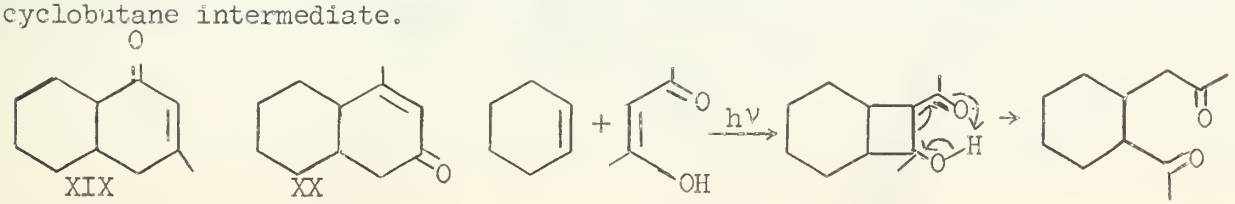
Corey has ingeniously used the photocycloaddition reaction in the syntheses of d,l-caryophyllene[15] (XVII) and α- caryophyllene alcohol (XVIII).[16] In the caryophyllene synthesis, the key intermediate was the 7,7-dimethyl bicyclo (4.2.0) octanone obtained by photolyzing cyclohexenone and isobutylene. Subsequent steps have been recently reviewed.[17] α- caryophyllene alcohol was prepared by the following sequence.



XVII

XVIII

In all the reactions presented thusfar, the photoadducts incorporated a stable cyclobutane. DeMayo has found, however, that in special cases the photocycloadducts may be quite labile and upon rearrangement yield some very interesting products.[18] Irradiation of acetyl acetone in cyclohexene led to the formation in high yield of a 1:1 adduct having infrared absorption of an unconjugated ketone and a strong nmr resonance for CH_3CO-. Treatment with dilute acid gave two isomeric unsaturated ketones identified as XIX and XX. Consequently the photoproduct was assigned structure XXI. Its formation can be rationalized by retroaldol opening of the expected cyclobutane intermediate.

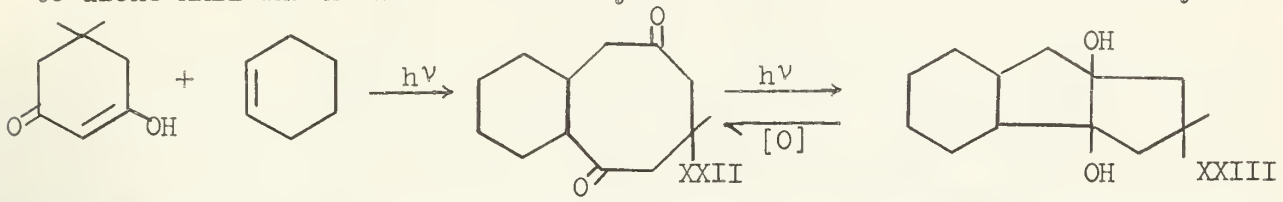


XIX XX XXI

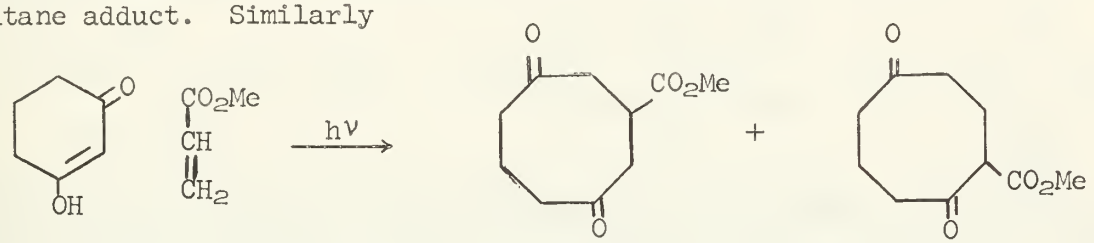
78%

No bicyclohexenyl, a common by-product of radical reactions in cyclohexene, was isolated here.

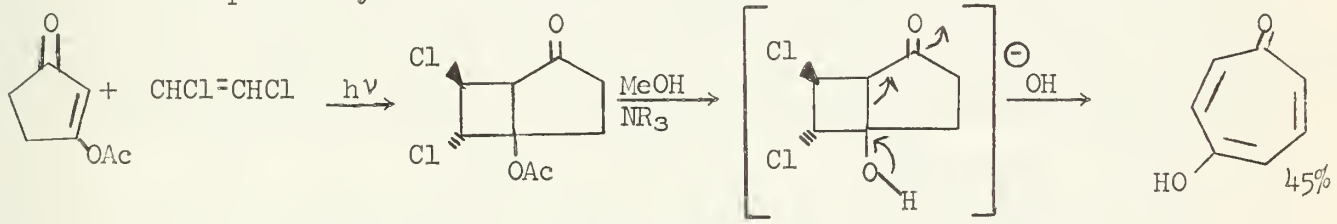
By extending this reaction, DeMayo has provided an easy entry into several difficultly accessible ring systems.[19] Irradiation of dimedone in cyclohexene leads to dione XXII which can be reduced by continued irradiation to the tricyclic diol XXIII.



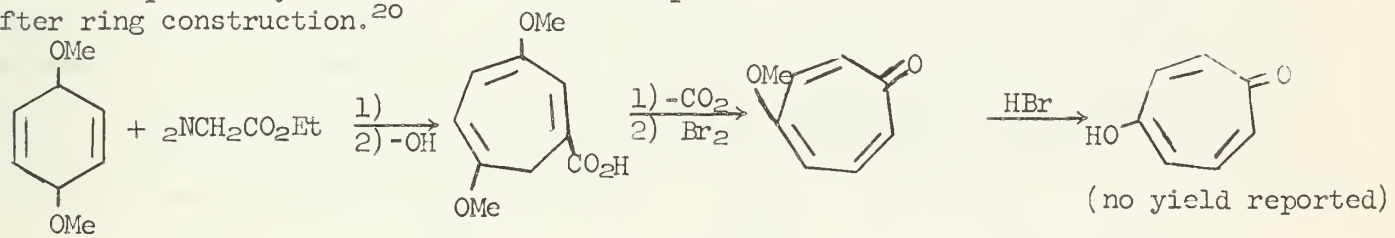
Here again the products can be rationalized by retroaldol opening of the initial cyclobutane adduct. Similarly



A convenient tropolone synthesis was also realized.

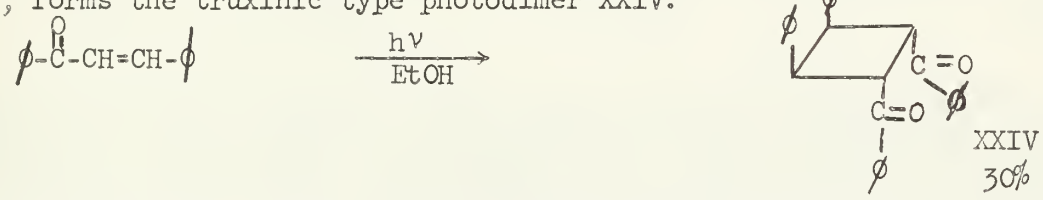


The inherent advantages of this procedure can be realized by comparison with a more common tropolone synthesis in which the required unsaturation must be introduced after ring construction.[20]



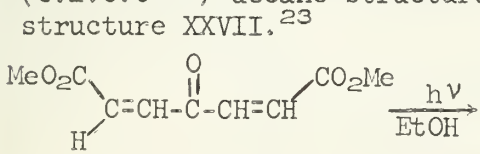
(no yield reported)

Photocycloadditions of Unsaturated Acyclic Ketones. - The photochemistry of alicyclic unsaturated keontes has been long known to form photodimers. Chalcone, for example, forms the truxinic type photodimer XXIV.[21]

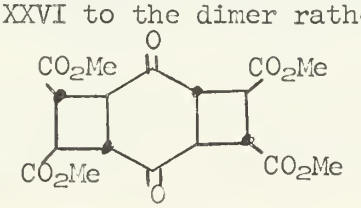


XXIV
30%

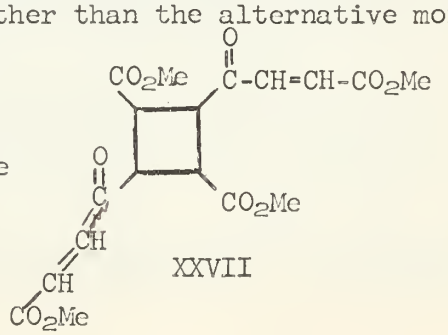
Solutions of dimethyl-3-keto-1,4-pentadiene-1,5-dicarboxylate (XXV) deposit a high melting dimer when exposed to sunlight.[22] Stobbe and Farber assigned the tricyclo (6.2.0.$0^{3,6}$) decane structure XXVI to the dimer rather than the alternative monocyclic structure XXVII.[23]



XXV



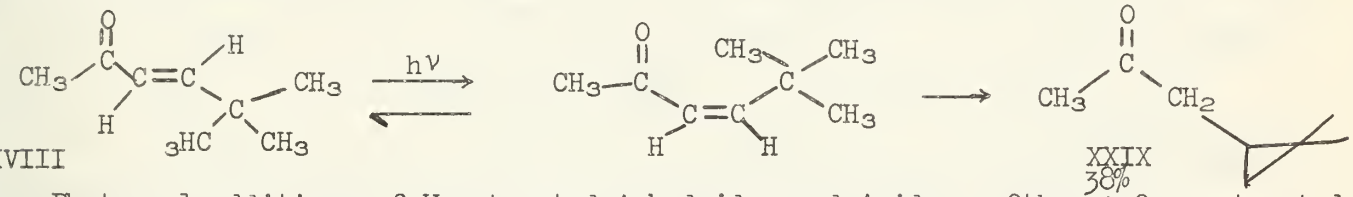
XXVI



XXVII

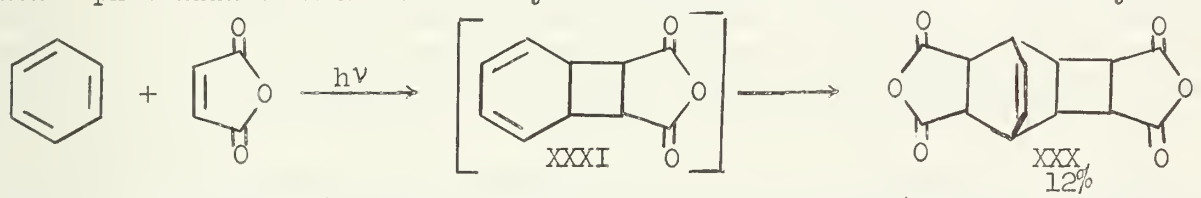
A recent reinvestigation of this reaction has substantiated Stobbe's structural assignment.[24] No infrared absorption for a conjugated carbonyl was seen nor were vinyl protons visible in the nmr.

Indication are strong though, that photolysis of alicyclic unsaturated ketones bearing no aromatic substitutents leads to quite different products than those observed with cyclic ketones. Most commonly, cis-trans isomerization about the double bond is noted.[25] Jorgenson and Yang found that photolysis of trans-5,5-dimethyl 3-hexene-2-one (XXVIII) caused ready isomerization to the cis isomer followed slow formation of a third ketone which was identified as acetonyl dimethyl cyclopropane (XXIX).[26] Independent synthesis confirmed the assignment. This clearly is not a cycloaddition reaction and could probably be best rationalized via a radical hydrogen abstraction mechanism.



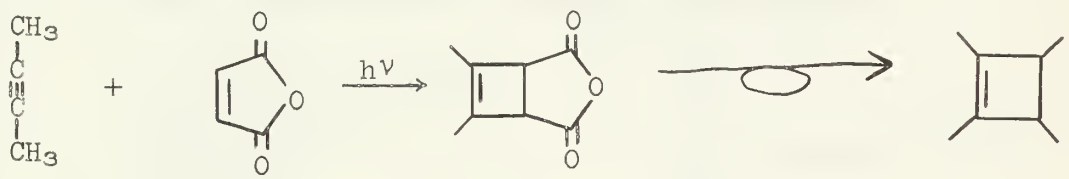
XXVIII XXIX 38%

Photocycloadditions of Unsaturated Anhydrides and Acids. - Other α,β-unsaturated carbonyl containing compounds such as anyhdrides and acids will undergo photocycloaddition with many substrates. Maleic anhydride has been extensively studied. Bryce-Smith and Lodge report the isolation of a stable 1:2 adduct of benzene and maleic anhydride which they identify as tricyclo (4.2.2.0) dec-7-ene, 3,4,9,10-tetracarboxylic acid dianhydride (XXX).[27] Reaction most probably proceeds thru formation of the cyclobutane photoadduct XXXI followed by thermal addition of the second anhydride unit.

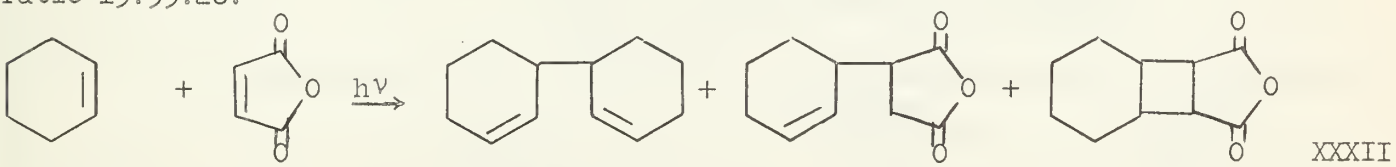


XXXI XXX 12%

Substituted benzenes (toluene, o-xylene and chlorobenzene) will form similar adducts and addition of benzophenone leads to a cleaner, more rapid reaction.[28] Using benzophenone sensitization, Schenck has obtained photoadducts of maleic anhydride with furan, thiophene, and numerous alkyl and halogen substituted olefins.[29] Criegee utilized this procedure with great success to prepare methyl substituted cyclobutenes for his thermal isomerization studies.[30]

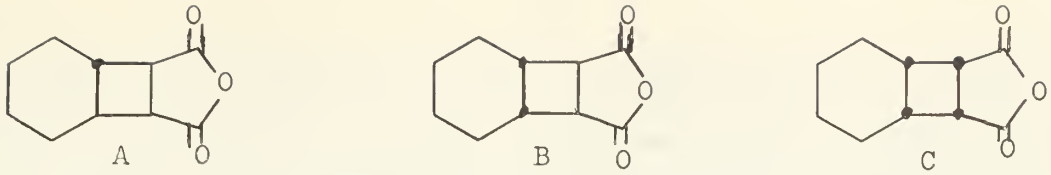


The existence of a charge transfer complex between maleic anhydride and benzene has been known for many years.[31] Irradiation of maleic anhydride in benzene through a filter which removed light of wavelength shorter than 280 mμ (the charge transfer complex has λmax = 278 mμ) led to photoaddition as before.[32] Barltrop and Robson found that selectively irradiating the cahrge transfer complex of cyclohexene and maleic anhydride at its absorption maximum led to photoadduct XXXII, bicyclo(4.2.0)-7,8-dicarboxylic acid anhydride, isolated as a mixture of three stereoisomers in the ratio 19:55:26.[33]



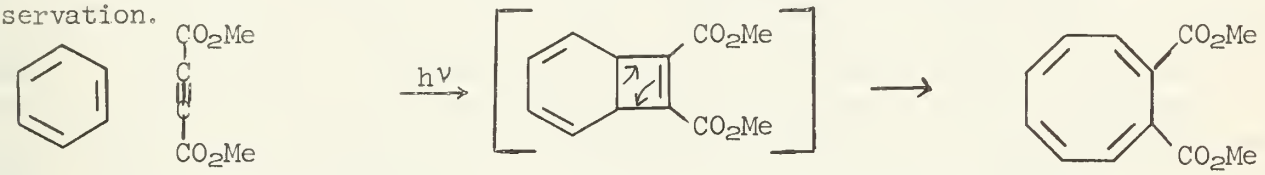
XXXII

These were identified by equilibration studies as the trans-cis (A), the cis-cis exo (B), and the cis-cis endo (C) isomers.



Isolation of bicyclohexenyl and cyclohex-2-enyl succinic anhydride are strong indications that a radical reaction occurred. This bicyclo diacid has also been prepared by unfiltered irradiation of methyl maleate in cyclohexene.[34] No evidence of charge transfer complex formation between the two reactants was found.

Dimethyl acetylene dicarboxylate has been added photolytically to benzene.[35] Instead of the expected bicyclo octene diester, however, cyclooctatetraene dicarboxylic ester was isolated. Valence isomerization of the expected adduct rationalizes this observation.



Benzophenone photosensitization has been reported unsuccessful here.[32]

The Mechanism of Photocycloaddition. - The photocycloadditions presented here were all characterized by the formation of a substituted cyclobutane whether stable or transient, but mechanistically these reactions are not quite so homogenous. The cyclic unsaturated ketones will be considered first. Ring size was seen to be important since cycloheptenone was unreactive and cyclooctenone first isomerized to a very reactive trans isomer which added thermally to olefins. Methyl substitution at the enone β carbon had no deleterious effect, but alkylation at the α carbon greatly reduced reaction rate and led to complex mixtures. Any postulated mechanism must also predict and explain the orientational specificity observed by Eaton and Corey and the preferential formation of adducts with the thermodynamically unstable trans 4-6 ring fusion.

Competition experiments conducted with several representative olefins in the presence of excited cyclohexenone suggest that the excited enone is mildly electrophilic since it reacted ten times faster with 1,1-dimethoxy ethylene than with isobutylene. Olefins substituted with strong electron withdrawing groups, e.g. acrylonitrile, were found to react very slowly.[13]

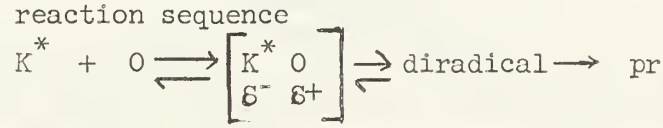
Table I

Olefin Competition for Excited 2-Cyclohexenone

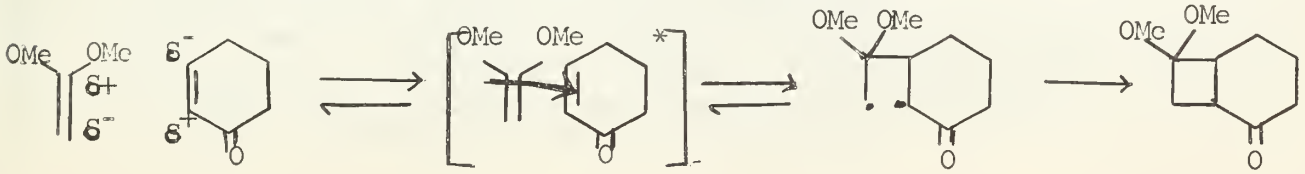
Olefin	Rel. Rate Factor
1,1-Dimethyloxy ethylene	4.66
Methoxy ethylene	1.57
Cyclopentene	1.00 (standard for study)
Isobutylene	0.40
Allene	0.234

Concerted cis addition of excited ketone to olefin appears unlikely since separate reactions of cyclohexenone with cis and trans 2-butene gave identical product mixtures.[13]

Corey has recently suggested that the experimental observations can be accomodated by the following reaction sequence



which can be illustrated by the reaction of 1,1-dimethoxy ethylene with cyclohexenone.

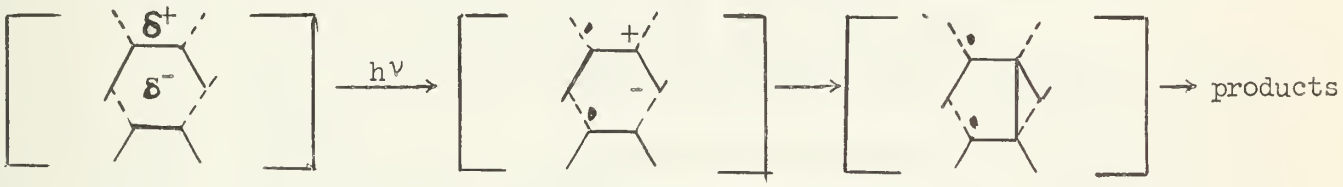


The diradical is estimated to have about 60 k.cal./mole excess energy above the cycloadduct, an amount quite sufficient to form the trans ring fusion. Little is known about the nature of the excited enone, but it is probably the $n\rightarrow\pi^*$ triplet formed by intersystem crossing from the initially formed $n\rightarrow\pi^*$ singlet. Triplet photosensitizers have not been tried in this reaction, but Eaton reports that cyclopentenone itself will replace acetophenone as a sensitizer in known triplet reactions.[36] Unfortunately neither phosphorescent nor fluorescent spectra have been observed for cyclohexone.[13]

This excited π-complex hypothesis is subject to some difficulties. No variation in the ultraviolet spectrum of cyclohexenone was observed when ethoxy ethylene was added. This concept also does not seem applicable to the photodimerization of cyclic enones where there is no apparent orientational specificity.[36]

Considerable work remains yet undone. The failure of cycloheptenone to undergo photocycloaddition is unexplained. Steric requirements for both olefin and ketone need to be established. Photosensitization studies might clarify the nature of the excited enone. Electron density requirements in the olefin could be explored.

Photocycloadditions of known charge transfer complexes are little better understood. Robson[33] has interpreted his findings with the maleic anhydride-cyclohexene system by the following scheme.



Photoexcitation here results in electron transfer from donor to acceptor followed by two step bond formation. The diradical is deemed sufficiently long-lived to allow ring inversion before final bond formation. Fumaronitrile and maleonitrile also form complexes with cyclohexene which yield similar photocycloadducts. The observed stereochemistry can be rationalized by this same procedure. It should be emphasized though that this scheme is a product rationalization and cannot be far extended. For example, unfiltered irradiation of methyl maleate in cyclohexene gives photoadducts, but the product distribution is not readily rationalized via this path.[33,34]

Some perplexing observations have been made regarding the photoaddition of maleic anhydride to benzene.[32] Cycloaddition initiated by selective irradiation (>280 mμ) was not oxygen sensitive, in fact, oxygenated reactions were much cleaner. The benzophenone sensitized reaction was quite different. Oxygen completely inhibited the reaction and light of wavelength less than 280 mμ was necessary. Irradiation through the filter as before gave no reaction when benzophenone was present even though it was shown that benzophenone did not interact with benzene, maleic anhydride or the charge transfer complex. It was concluded that two different reaction pathways were operative.

Conclusion. - Photocycloaddition has been shown to be a flexible synthetic tool providing easy entry into difficultly accessible cyclic systems. Considerable work in extending the scope of this reaction and elucidating its mechanism remains to be done.

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MECHANISM OF THE BROMINE OXIDATION OF ALDEHYDES

Reported by R. P. Quirk April 29, 1965

Introduction: The use of halogens as oxidizing agents dates back to 1861 when Hlasiwetz[1] oxidized lactose with bromine. Subsequently, halogen oxidations have found wide application in the carbohydrate field for both preparative and analytical proposes;[2,3,4] however, definitive mechanistic studies on these halogen oxidations have only appeared recently. The diverse applications of the bromine oxidation reaction include the dehydration of tertiary alcohols,[5] the oxidative decarboxylation of the silver salts of carboxylic acids,[6] the selective phenol oxidation-peptide cleavage reaction,[7,8] the oxidative degradation of imidazoles,[9] the selective oxidation of the hemiacetal linkage in carbohydrates to lactones,[10] and the oxidation of alcohols[11] and aldehydes. This seminar will attempt to correlate all of the available information pertaining to the bromine oxidation of aldehydes in acidic solution with a general mechanistic scheme which might serve as a model for the bromine oxidation of carbohydrates. A pertinent review by Barker[12] dealing with the kinetic studies on the oxidation of organic compounds with halogens has recently appeared.

General considerations: The complications which should be kept in mind while evaluating the experimental work on the bromine oxidations of aldehydes are the following: the fact that several different oxidizing agents may exist in aqueous bromine solutions depending upon the pH; the possibility that the mechanism may vary with the substrate and the reaction conditions; and the presence of aldehyde hydrate in equilibrium with the free aldehyde, either or both of which may be oxidized by bromine.

Kinetic results and the nature of the active oxidizing agent: In 1904 Bugarszky[13] found that the rate equation for the oxidation of acetaldehyde by bromine in unbuffered aqueous solution could be expressed as

$$-d[Br_2]/dt = k[Br_2][RCHO]$$

where $[Br_2]$ is equal to the molar concentration of bromine in solution, [RCHO] is the total molar concentration of aldehyde, and the experimentally observed rate constant, k, was equal to 1.20 l/mole-min. at 25° C. The rate of the reaction was followed by titrating the molecular bromine iodometrically and the bromide ions by the Volhard method. The products of the reaction were acetic acid and hydrobromic acid in accord with the stoiciometric equation

$$CH_3CHO + H_2O + Br_2 \longrightarrow CH_3CO_2H + 2HBr$$

Bugarszky's observation that the apparent rate constant decreased with increasing reaction time can be explained by means of the equilibrium

$$Br_2 + Br^- \underset{}{\overset{K_{eq}}{\rightleftharpoons}} Br_3^-$$

where K_{eq} is equal to 17 l. mole^{-1} at 25° C.,[14] and the fact that the tribromide ion was inactive with respect to oxidation of acetaldehyde.[15]

When the oxidation of acetaldehyde was performed in the presence of ethyl alcohol (the acetaldehyde was an intermediate reaction product in the oxidation of a 41% solution of ethanol), Farkas[16] found that the reaction products were ethyl acetate and acetic acid in a ratio of about 2.2/1.0; the reaction conditions were chosen so that catalysis of the esterification reaction was negligible. In addition, when methyl alcohol was present in the reaction mixture under conditions where the rate of oxidation of methanol by bromine, as well as the rates of esterification and transesterification are negligibly small, methyl acetate was found to be one of the reaction products. These observations led Farkas to suggest that acetaldehyde reacted in its hydrated form in aqueous solution and primarily in its hemiacetal form in alcoholic solution.

Lichtin[17] considered the possibility that acetyl bromide was an intermediate in the reaction of acetaldehyde with bromine in aqueous ethanol. The observed kinetics were regarded as being consistent with a mechanism in which acetyl bromide would be rapidly solvolyzed to a mixture of acid and ester. However, the ratio of ethyl acetate to acetic acid produced by the action of 41% aqueous ethanol on acetyl

bromide was equal to 0.64, whereas the value of 2.2 is found in the oxidation reaction. Thus, the reaction does not appear to involve acetyl bromide as an intermediate.

Perlmutter-Hayman and Weissmann[15] conducted a pertinent experiment on the rate of oxidation of acetaldehyde by hypobromous acid. Hypobromous acid is formed from molecular bromine in aqueous solution according to the equilibrium

$$Br_2 + H_2O \underset{}{\overset{K_{eq}}{\rightleftharpoons}} HOBr + HBr$$

for which K_{eq} is equal to 5.8×10^{-9} at 25° C.[18] The rate of the oxidation reaction using hypobromous acid was found to be initially very slow and to increase as the reaction proceeded. The increase in rate corresponded to the liberation of bromine which qualitatively showed that $k_{Br_2} > k_{HOBr}$. Extrapolation to time t = 0 gave values of k_{HOBr}/k_{Br_2} of 1/50 at lower values of pH and 1/200 at a pH of 7.6. While attempting to determine the rate of oxidation with hypobromous acid in the absence of free bromine, silver ions were added to the reaction mixture; however, it was found that silver ions accelerated the reaction.[15,16] Although these results are only qualitative, they show that oxidations by bromine in acid solution will not be affected by the small amount of hypobromous acid present. This effect will also decrease as the reaction proceeds and forms bromide ions.

Consideration of the bromate-bromine equilibrium

$$BrO_3^- + 6\,H^+ + 5Br^- \underset{}{\overset{K_{eq}}{\rightleftharpoons}} 3Br_2 + 3\,H_2O$$

for which a K_{eq} equal to 6×10^{33} has been calculated,[19] indicates little contribution to be expected for the bromate ion in acidic solution. Farkas[19] has shown that the reaction of bromate with alcohol proceeds at a negligibly small rate in moderately acidic solutions. When the oxidation reaction was run in the presence of both bromine and bromate, Farkas found that the total bromine titer underwent little change and the pH remained constant as a result of the previous equilibrium.

Isotope effects: Kaplan[20] estimated the primary deuterium isotope effect for the oxidation of acetaldehyde-1-d while determining the isotope effect for the oxidation of ethanol-1,1-d_2 by bromine in aqueous solution. The oxidation of ethanol by bromine takes place in two stages[16]

$$CH_3CH_2OH + Br_2 \xrightarrow{k_I} CH_3CHO + 2HBr$$

$$CH_3CHO + H_2O + Br_2 \xrightarrow{k_{II}} CH_3CO_2H + 2HBr$$

The ratio of the rate constant for reaction II to that for reaction I can be determined, under appropriate conditions, by measuring the steady-state concentration of acetaldehyde during the oxidation of ethanol. If this ratio is measured for each of the isotopic alcohols, it is possible to calculate the isotope effect for the oxidation of acetaldehyde from the relationship

$$k_{II}^H \Big/ k_{II}^D = \frac{k_{II}^H / k_I^H}{k_{II}^D / k_I^D} \times k_I^H \Big/ k_I^D$$

The isotope effect for the oxidation of ethanol (k_I^H/k_I^D) was determined by using concentrations of alcohol in considerable excess relative to the concentration of bromine. From the values $k_{II}^H/k_I^H = 182$, $k_{II}^D/k_I^D = 201$, and $k_I^H/k_I^D = 4.3$, the value of k_{II}^H/k_{II}^D was calculated to be 3.9. The similarity between the isotope effect ($k_H/k_D = 4.3$) for the oxidation of ethanol and the value above for the oxidation of acetaldehyde was regarded by Kaplan as an indication that these reactions have similar mechanisms, i.e., the aldehyde reacting in the form of its hydrate or hemiacetal.

In a study of the acid-catalyzed bromination(enolization) of some aldehydes in aqueous solutions, McTigue and Sime[21] determined the contribution of the uncatalyzed bromine oxidation to the reaction. It was observed that in the pH range 1-5, the rate of enolization is negligible compared with the rate of oxidation. McTigue and Sime extended their studies to include the solvent isotope effect on the reaction

rate in an attempt to determine whether the free aldehyde or the hydrated aldehyde was the reacting species. The observed rate constants in D_2O and H_2O are listed in Table I., together with the hydration equilibrium constants determined by Gruen and McTigue[22] for these solvents.

Table I.

Rate constants for the bromine oxidation of aldehydes and hydration equilibrium constants in D_2O and H_2O

aldehyde	10^2k (l./mole-sec.) at 25°		equilibrium constants at 25°	
	H_2O	D_2O	H_2O	D_2O
HCHO	0.51	----	1000	----
CH_3CHO	1.51	0.49	0.93	1.11
CH_3CH_2CHO	3.98	1.21	0.69	0.80
$CH_3CH_2CH_2CHO$	4.22	1.31	0.48	0.57
$(CH_3)_2CHCHO$	6.73	2.10	0.44	0.55
ØCHO	2.69	2.08	----	----
CCl_3CHO	----	----	28000	33000

Bell and coworkers[23] studied the kinetics of the hydration of acetaldehyde in aqueous solution by a thermal maximum method devised by Bell and Clunie.[24] The half-times for the general acid-base catalyzed reaction ranged from 0.3 to 60 seconds at 25°C. Thus, the kinetics of the bromine oxidations should not be affected by the kinetics of the hydration reaction.

McTigue and Sime[21] used the hydration equilibrium constants and the rate constants referring to the analytical aldehyde concentration to calculate rate constants referring to both the free aldehyde and its hydrate. These calculated rate constants are listed in Table II, together with the corresponding solvent isotope effects.

Table II.

Calculated rate constants(l./mole-sec.), and solvent isotope effects

Aldehyde	10^2k_A	10^2k_H	$(k_{H_2O}/k_{D_2O})_A$	$(k_{H_2O}/k_{D_2O})_H$
HCHO	480	0.51	----	----
CH_3CHO	2.49	3.84	2.7	3.7
CH_3CH_2CHO	6.21	11.1	2.6	3.7
$CH_3CH_2CH_2CHO$	5.95	14.5	3.1	3.7
$(CH_3)_2CHCHO$	9.36	24.0	3.3	3.7
ØCHO	2.69	----	1.3	----

where the subscripts A and H refer to the free aldehyde and the hydrated aldehyde, respectively. McTigue noted that the rate constants in the k_H series showed a "regular trend" when the logarithms of the rate constants were plotted against Taft's[25] polar substituent constants, σ^*, for the alkyl groups. Taft's σ^* values are a measure of the inductive electron donating ability of an alkyl substituent in the absence of steric and conjugative effects. This correlation and the large solvent isotope effect (3.7) listed in Table II support the previous qualitative assumption by Farkas[16] that the aldehyde hydrate is the reactive species. The large solvent isotope effect was regarded as being too great to be due to a medium effect and implied a proton transfer in the rate determining step. This can be compared with the isotope effects found by Reitz[26] for the rate-determining enolization[27] of nitromethane, listed in Table III.

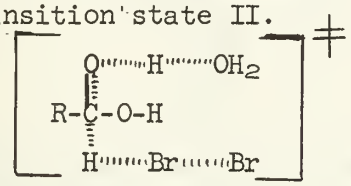
Table III.

Enolization of nitromethane

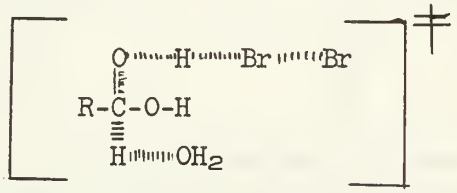
compound	solvent	$10^6 k_B$ (l./mole-min) at 70°	isotope effects k_H/k_D	k_{H_2O}/k_{D_2O}
CH_3NO_2	H_2O	3.21		
CH_3NO_2	D_2O	1.90		1.7
CD_3NO_2	H_2O	0.85	3.8	
CD_3NO_2	D_2O	0.37	5.1	2.3

Although it is a C-H bond which is being broken in these reactions, this model reaction which also exhibits general base-catalysis indicates that it might be possible to distinguis medium effects from primary isotope effects in these systems.

In view of Kaplan's[20] observation of a primary isotope effect on the alpha C-H bond together with the observed solvent isotope effects, McTigue[21] proposed the transition state I for the oxidation of aliphatic aldehydes; however, the kinetics do not eliminate transition state II.



I.



II.

McTigue noted that this mechanism required that the reaction exhibit general base catalysis.

The lower solvent isotope effect(1.3) observed for the oxidation of benzaldehyde was regarded as being consistent with a medium effect and suggested a different mechanism consistent with the observation that benzaldehyde is not measurably hydrated in aqueous solution. The proposed mechanism is

$$\phi CHO + Br_2 \xrightarrow{\text{slow}} \phi\overset{+}{C}O + HBr + Br^-$$

$$\phi\overset{+}{C}O + H_2O \xrightarrow{\text{fast}} \phi CO(\overset{+}{O}H_2)$$

$$\phi CO(\overset{+}{O}H_2) + \xrightarrow{\text{fast}} \phi CO_2H + H^+$$

Cox and McTigue[28] have recently verified the prediction that the oxidation of aliphatic aldehydes should be subject to general base catalysis. The observed rate constants were linear with concentration of acetate ion at a constant ionic strength of 0.2 and for a constant acetate-acetic acid buffer ratio. Figure 1 shows the results for the oxidation of acetaldehyde, propionaldehyde, and isobutyraldehyde in acetate buffer solutions.

Figure 1. Variation of reaction rate with buffer concentration. (a) isobutyraldehyde; (b) propionaldehyde; (c) acetaldehyde.

The rate law for this reaction showing general base catalysis is

$$-d[Br_2]/dt = k_e[Br_2][RCHO]$$

where k_e is the experimentally observed rate constant

$$k_e = k_o + k_{OH^-}[OH^-] + k_B[B]$$

where k_o is the rate constant for the solvent catalyzed reaction, k_{OH^-} is the rate constant for the OH^- catalyzed reaction, and k_B is the rate constant for the base catalyzed reaction for base B. The values for k_o and the catalytic constants k_{OH^-} were estimated from the intercepts of the plots of rate constant versus buffer concentration. The catalytic constants referred to aldehyde hydrate concentration are listed in Table IV.

Table IV.

Catalytic constants for the general base catalyzed bromine oxidation of aliphatic aldehydes.

aldehyde	10^2k_o (l/mole-sec)	$10^2k_{OAc^-}$ (l^2/mole^2-sec)	$10^7k_{OH^-}$ (l^2/mole^2-sec)
HCHO	0.51	0.68	3
CH_3CHO	2.95	11.0	>3
CH_3CH_2CHO	8.18	28.4	>3
$(CH_3)_2CHCHO$	18.7	42.5	>3

Cox and McTigue also carried out the oxidation of propionaldehyde with acetate buffers in both D_2O and H_2O. The isotope effects on the catalytic constants referred to the concentration of aldehyde hydrate were as follows:

$$k_o(H_2O)/k_o(D_2O) = 2.2; \quad k_{OAc^-}(H_2O)/k_{OAc^-}(D_2O) = 3.9$$

Although the isotope effect for the solvent catalyzed reaction could represent a medium effect, the isotope effect observed for the acetate catalyzed reaction is indicative of a proton transfer in the rate determining step; however, this isotope effect is ambiguous because it was measured in two different solvent systems. The solvent isotope effect for the acetate-catalyzed reaction compares very favorably with the corresponding primary isotope effect observed for the enolization of acetone, where k_H/k_D for the acetate-catalyzed enolization was equal to 3.76.[27] The relative magnitudes of these isotope effects are also consistent with Swain's[27] observation that the isotope effects for base-catalyzed enolizations increased with increasing basicity of the attacking base. This effect has been explained in terms of an increase in the transition state symmetry[29] and thus maximum isotope effect as the bond strengths in the starting and final states are more nearly equal.[30]

Cox and McTigue were able to account for the anomolous negative salt effect observed by Overend, Barker, and Rees [31] in terms of the decrease in hydrate concentration accompanying the addition of neutral salts.

Thus, the observation of general base catalysis, the large solvent isotope effect, and Kaplan's[20] primary isotope effect provide strong evidence for a mechanism involving synchronous removal of a hydride ion and a proton from the aldehyde hydrate. The suggested mechanism is

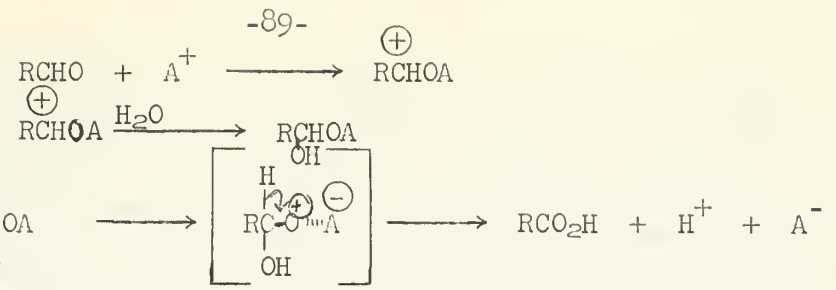
$$RCHO + H_2O \rightleftharpoons RCH(OH)_2 \qquad \text{equilibrium}$$

$$RCH(OH)_2 + Br_2 + B \longrightarrow RCO_2H + BH^+ + HBr_2^- \qquad \text{rate determining}$$

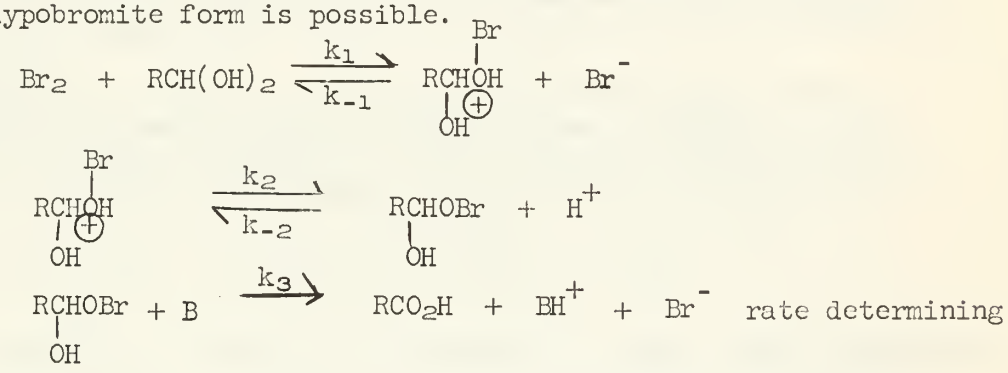
$$HBr_2^- \longrightarrow H^+ + 2Br^-$$

where the second and third steps can occur synchronously. The final proof that the reactive species in aqueous solution is the aldehyde hydrate, as well as the determination of the O-H isotope effect, awaits determination of the reaction kinetics in non-aqueous solution. The anomolous behavior of benzaldehyde indicates that the free aldehyde may also react with the bromine; this possibility has not been considered in the literature to date.

Hypobromite mechanism: While expounding on the common basis of organic oxidations in acidic solution, Levitt[32] proposed the following general mechanism for the oxidation of aldehydes.



where A^+ is a positive ion or a neutral molecule containing one relatively positively charged atom. If the aldehyde hydrate is the reacting species, a similar mechanism involving an intermediate hypobromite form is possible.



After a steady state treatment of the two hypobromite-type intermediates, the resulting rate expression is

$$-d[Br_2]/dt = \frac{k_1k_2k_3[RCHO][Br_2][B]}{k_{-1}k_{-2}[H^+][Br^-] + k_{-1}k_3[B][Br^-] + k_2k_3[B]}$$

Aside from the analogies which can be drawn from other oxidation mechanisms, there are several chemical observations which support this type of reaction sequence. Chattaway[33,34] was able to prepare primary, secondary, and tertiary hypochlorites from the corresponding alcohols and chlorine in strongly basic solution. He found that only the tertiary hypochlorites were stable, however; the primary and secondary hypochlorites decomposed rapidly into aldehydes and ketones on warming to room temperature. Arnett[35] has recently reported the first preparation of a secondary hypobromite, 4,4'-dimethoxydiphenylmethyl hypobromite, by treatment of the alcohol with hypobromous acid. When this compound was allowed to stand in a neat condition, it quickly decomposed to the corresponding benzophenone. The obvious conclusion is that organic hypohalites decompose into oxidation products. It should be emphasized, however, that even though hypohalites decompose into the corresponding oxidation products, this does not have to be the major or even a contributing pathway under acidic oxidizing conditions for alcohols or aldehydes. Arnett's work indicates that the answer should be available in the near future for the alcohols, at least.

It is difficult to reconcile the observed kinetics with the formation of an intermediate hypobromite. The first step would probably be reversible in view of the kinetics observed by Anbar[36] for the formation and hydrolysis of t-butyl hypochlorite. The equilibrium constant ($k_{hydrolysis}/k_{formation}$) was found to be equal to 0.24. The reaction exhibited general acid-base catalysis. The facile hydrolysis of hypobromites is also apparent from Arnett's[35] work. Arnett found that 4,4'-dimethoxydiphenylmethyl hypobromite was solvolyzed to the benzhydrol and its acetate in 80% aqueous acetic acid. Another reaction which would have to be considered if the hypobromite were an intermediate is the reaction of the hypobromite with bromide ions; i.e.,

Reactions of this type have been discussed by Anbar;[37] for example, acetyl hypobromite is unstable in the presence of bromide ions due to the above type of equilibrium. Because of the observations that bromide ions only affect the amount of free bromine in equilibrium with the tribromide ion and that the reaction is independent of acid concentration (see Figure 2), the hypobromite mechanism would give the observed

kinetics only if the terms involving $[H^+]$ and $[Br^-]$ were neglibible relative to the "k_2k_3" term. An example of the extreme insensitivity of the rate of bromine oxidation of aldehydes to acid concentration has been reported by McTigue and Sime.[38] They found that the rate of oxidation of formaldehyde was constant in the acidity range from -1.0 to -5.0 H_0 units, but then decreased with increasing acidity due to protonation of the formaldehyde. Thus, the chemistry of hypohalites does not seem to be in accord with the assumptions regarding rate constants which would have to be made to obtain the observed kinetics. Probably the best reason for accepting the concerted reaction pathway is the large solvent isotope effects observed by McTigue and coworkers.[21,28] These isotope effects indicate a proton transfer from the aldehyde hydrate oxygen in the rate determining step. This is not compatible with the formation of an intermediate hypobromite.

Aldehyde hydrate anion reaction: Although the catalytic constants k_{OH^-} listed in Table IV were measured only approximately, these constants seem to behave in a different manner than the other catalytic constants. This difference in behavior could be due to the onset of the kinetically indistinguishable oxidation of the aldehyde hydrate anion. Thus,

$$RCH(OH)_2 + OH^- \rightleftharpoons RCH(O^-)OH + H_2O$$

$$RCH(O^-)OH + Br_2 \longrightarrow RCO_2H + HBr_2^- \quad \text{rate determining}$$

$$HBr_2^- \longrightarrow H^+ + 2Br^-$$

Perlmutter-Hayman and Weissmann[15] invoked a reaction pathway involving oxidation of the anion of acetaldehyde hydrate to explain their observation that the rate constants increased with increasing pH as shown in Figure 2.

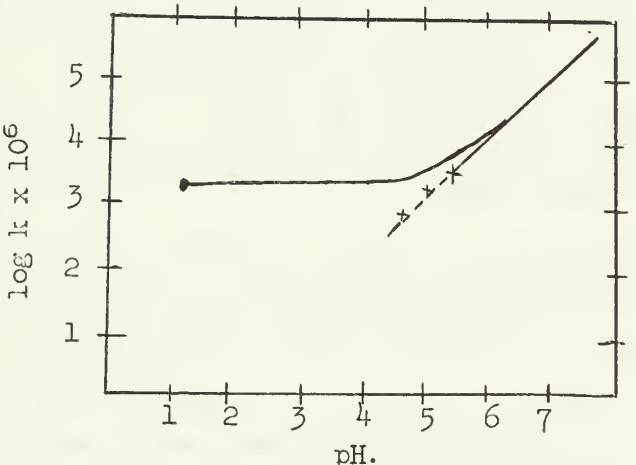


Figure 2. - The dependence of the logarithm of the rate constant on pH.

In the oxidation of chloral hydrate by bromine, McTigue[39] observed no general base catalysis, but specific hydroxyl ion catalysis. Presumably this hydroxyl ion catalyzed path involved the chloral hydrate anion, although no quantitative data other than the pK_a values obtained by Bell[40] listed in Table V. are available.

Table V.

Acidity constants of certain aliphatic aldehydes

Aldehyde hydrate	pK_a
$CH_2(OH)_2$	13.27
$CH_3CH(OH)_2$	13.57
$Cl_3CH(OH)_2$	10.04

Carbohydrates: The close similarity between aldehyde hydrates and the hemiacetal forms of the carbohydrates has led many researchers to regard the mechanism of their bromine oxidations as being similar.[12,41] However, the bromine oxidation of carbohydrates is complicated by competing epimerization and the possibliity of neighboring

group participation in the transition state. It is expected that general base catalysis should also appear in this reaction. This presumption is fortified by the report by Lichtin and Saxe[42] that the oxidation of glucose by chlorine was accelerated by added concentrations of buffer anions. Although it is tempting to blithely conclude that the bromine oxidations of aldehydes and carbohydrates probably proceed by the same general mechanism, certain anomalies recently observed in the bromine oxidation of glucose[31] caution against such a premature conclusion. The chemistry of hypohalites shows that under certain conditions the formation of this intermediate could be a major pathway in the oxidation mechanism.

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ACID CATALYZED DECOMPOSITION OF DIPHENYLDIAZOMETHANE IN ETHANOL

Reported by George Su May 3, 1965

Introduction. The reactions of diphenyldiazomethane (DDM) with acids have been widely employed to investigate the sigma-rho correlations for a variety of acids.[1-5] A considerable amount of research has been prompted by the controversy concerning diazonium ion and hence carbonium ion intermediates for these reactions as well as for deamination reactions.[6] An examination of the reaction mechanism thus seems warranted.

Deamination reactions and the chemistry of diazo compounds have been extensively reviewed.[6,7,8,9] Hence the main topic discussed in this abstract will be the reaction of DDM with weak acids in ethanol (Eq. 1).

$$(C_6H_5)_2CN_2 + HA \xrightarrow{EtOH} (C_6H_5)_2CHA + (C_6H_5)_2CHOEt + N_2 \quad (1)$$

Although a fair amount of work has been done on the kinetics and mechanism of the acid catalyzed solvolysis reactions of diazoacetic ester and reactions of DDM with acids in non-hydroxylic solvents,[10] comparatively little work was done before 1950 on the reactions of DDM with acids in ethanol. In the early 1950's Roberts and coworkers[11,12,13] first launched a systematic effort to study the kinetics and mechanism of these reactions.

Some Preliminary Experimental Observations. Roberts and coworkers[11] found that DDM reacts smoothly with ethanol to give benzhydryl ethyl ether in the presence of p-toluenesulfonic acid in 95% yield. The other 5% consists of diphenylketazine, $\phi_2C{=}N{-}N{=}C{-}\phi_2$, and tetraphenylethylene. There was no reaction in the absence of an acid. If light or heat was used instead of acid as a catalyst, diphenylketazine becomes the major product.[14]

In non-hydroxylic solvents, DDM reacts with carboxylic acids to give almost quantitative yields of benzhydryl esters.[14,15] However, in ethanol, carboxylic acids such as benzoic acid were found to react with DDM to give about 60% benzhydryl benzoate and 40% benzhydryl ethyl ether.[12] The 60:40 ester to ether ratio was later found to hold for a large number of acids.[16-19]

It was further noted[11] that the reaction was accurately first order in DDM and first order in acid except at very low acid concentrations (below 0.00025M) where some irregularities in reaction order appear. The irregularities do not follow any definite trend, and could be due to trace amounts of basic impurities.

The reaction was not catalyzed by base.

General Acid Catalysis. For the p-toluenesulfonic acid (strong acid) catalyzed reaction of DDM with ethanol,[11] the second order rate was found to drop sharply upon addition of water to ethanol. This effect has been attributed to the conversion of ethyloxonium ion to hydronium ion[20] according to the following equation:

$$C_2H_5\overset{\oplus}{O}H_2 + H_2O \rightleftharpoons C_2H_5OH + \overset{\oplus}{H_3O} \quad (2)$$

If the reaction proceeds by general acid catalysis, the decrease in rate could simply be explained by assuming that the hydronium ion has a lower catalytic efficiency than ethyloxonium ion.

Picric acid reacts with DDM in ethanol to give only benzhydryl ethyl ether.[11] The absence of benzhydryl picryl ether could be rationalized by the steric and electronic effects of the nitro groups. The kinetic results of the reaction at constant picric acid concentration and constant ionic strength, but varying picrate ion concentration are shown in Table I.

Table I

Effect of % Dissociation of Picric Acid on Reaction Rate

Picric acid = 0.000715M/l; μ = 0.100

Li Picrate Mole/l	$H^{\oplus}$ Mole/l	Calc. Conc. of undissoc. acid Mole/l	% Dissoc. of Picric acid	k $min.^{-1}$
0.0000	0.000608	0.000107	85.0	0.224
0.0333	0.000065	0.000650	10.0	0.212
0.0667	0.000035	0.000680	5.2	0.212
0.1000	0.000025	0.000690	3.6	0.211

It is clear from the data summarized in Table I that there is virtually no change in rate constant going from 85% to 4% dissociation of picric acid. If the solvated hydrogen ion, that is, the ethyloxonium ion were the only species that catalyzes the reaction, there should be a substantial change in reaction rate for such a change in the fraction of dissociation. These observations can reasonably be explained by invoking general acid catalysis, that is, by postulating that both ethyloxonium ion and picric acid act as catalysts for the reaction, and that the catalytic constant of picric acid is slightly lower than that of ethyloxonium ion.

The reaction rate between DDM and benzoic acid in ethanol is increased by the addition of water. This can be due to two things: (1) medium effect; and (2) increase in the dissociation of benzoic acid, thereby increasing the concentrations of ethyloxonium ion and hydronium ion. Most likely both (1) and (2) contribute to the increase in rate. That there is a medium effect is borne out by the fact that addition of nitrobenzene also increases the rate of the reaction.[11] That increase in the dissociation of benzoic acid also increases the reaction rate is demonstrated by the following experiment.[11] It was found that in 82.5% ethanol-17.5% water, addition of benzoate ion causes a sharp decrease in rate which soon levels off (Fig. 1). This is consistent with the Mass Law suppression of benzoic acid dissociation, thereby reducing the concentrations of ethyloxonium ion and hydronium ion, both of which have a higher catalytic constant than benzoic acid.

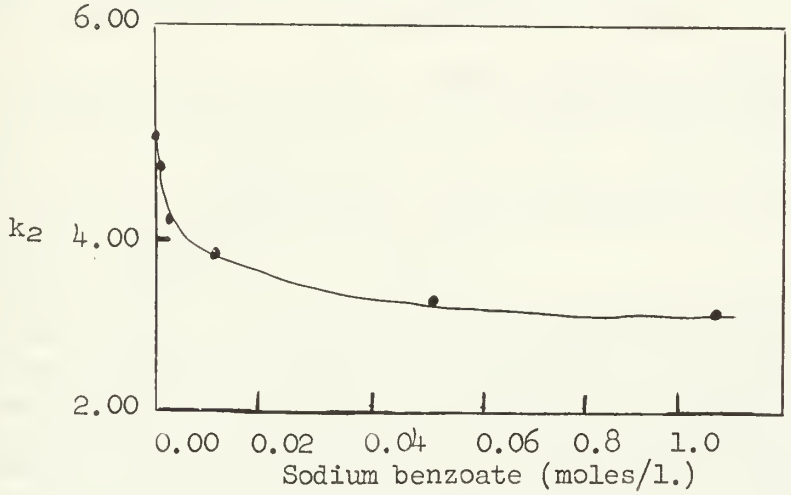


Fig. 1

Effect of benzoate ion on the rate constant of DDM-benzoic acid reaction in aqueous ethanol.

Compelling evidence in favor of general acid catalysis is the observed kinetic isotope effect for the p-toluenesulfonic acid catalyzed reaction of DDM in aqueous ethanol.[11] It was found that in 82.5% ethanol-17.5% water, the replacement of 38% of the O-H groups by O-D groups resulted in a 31% decrease in rate. It is generally true that specific acid catalysis is speeded up by deuterium substitution whereas general acid catalysis is slowed down by deuterium substitution.[21] Thus it seems that there is little doubt that the reactions of DDM with acids in ethanol proceed by general acid catalysis.

Consequences of General Acid Catalysis. Perhaps the most important consequence of general acid catalysis is that is helps eliminate a number of possible mechanisms. General acid catalysis makes it possible to limit the reaction mechanism to two general categories: 1) Rate determining proton transfer from general acid to substrate; and 2) a reversible hydrogen bonding between the acidic hydrogen of the general acid and the substrate followed by a rate determining reaction of the complex.

As mentioned earlier, the reaction is first order in DDM and first order in acid or second order overall. The rate equation is:

$$-\frac{d(DDM)}{dt} = k_2(HA)(DDM) \quad (3)$$

Since two products are formed, viz., the combined product of acid and DDM (ester) and benzhydryl ethyl ether (ether), k_2 might be separated into two parts: $k_{\frac{1}{2}}$ which

consumes the acid to give the ester, and k_2'' which gives the ether. Thus Eq. (3) can be rewritten as:

$$-\frac{d(DDM)}{dt} = (k_2' + k_2'')(HA)(DDM) \quad (4)$$

or

$$\frac{dx}{dt} = k_2\left(a - \frac{k_2'x}{k_2}\right)(b-x) \quad (5)$$

where a = initial concentration of the acid, b = initial concentration of DDM, and x = concentration of the products.

Roberts and co-workers[12] noted that the reaction rates follow Eq. 5 closely and that the values of k_2'/k_2 obtained from the rate data agreed, within experimental error, with values calculated from acidimetric determinations of the acid consumed.

If the proton transfer is the rate determining step, equation (4) or (5) are consistent with two mechanisms, one involving a common intermediate, and the other involving parallel reaction paths as in equations (6) and (7), respectively.

$$(C_6H_5)_2CN_2 + HA \longrightarrow (C_6H_5)_2CHN_2^{\oplus}\,A^{\ominus} \longrightarrow (C_6H_5)_2CH^{\oplus}\,A^{\ominus} \xrightarrow{EtOH} \text{ether}$$
$$\text{ester} \quad (6)$$

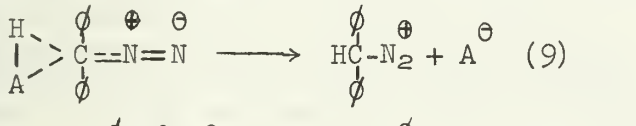
$$HA + EtOH \rightleftharpoons EtOH_2^{\oplus} + A^{\ominus} \xrightarrow{(C_6H_5)_2CN_2} (C_6H_5)_2CHN_2^{\oplus} + EtOH \longrightarrow (C_6H_5)_2CH^{\oplus} \xrightarrow{EtOH} \text{ether}$$
$$\downarrow (C_6H_5)_2CN_2 \qquad (C_6H_5)_2CHN_2^{\oplus}\,A^{\ominus} \longrightarrow (C_6H_5)_2CHA^{\oplus\ominus} \longrightarrow \text{ester.} \quad (7)$$

If the decomposition of complex formed from the acid and substrate (a single step process) is the rate determining step, then equation (4) or (5) is consistent only with equation (8).

$$HA + EtOH \rightleftharpoons EtOH_2^{\oplus} + A^{\ominus} \underset{}{\overset{(C_6H_5)_2CN_2}{\rightleftharpoons}} [EtOH_2\cdot(C_6H_5)_2CN_2]^{+} \longrightarrow \text{ether}$$
$$\downarrow (C_6H_5)_2CN_2 \qquad [HA\cdot(C_6H_5)_2CN_2] \longrightarrow \text{ester.} \quad (8)$$

From equation (6), the relative amounts of ether and ester would depend on the tendency of the ion pair to dissociate or collapse respectively. From equation (7), or (8) the same ratio would depend on the difference in activation energies of the two competing reactions. It will be shown later that the product ratios of this particular reaction is very sensitive to activation energy differences.

The mode of proton transfer has not been carefully studied. Two or three processes, depending on whether a phenolic or a carboxylic acid is involved, have been proposed.[12,17] The two processes for phenolic acids are as follows:



$$\text{or} \quad A\cdots H\cdots C(\phi_2)-N=N \longrightarrow H-C(\phi_2)-N_2^{\oplus} + A^{\ominus} \quad (10)$$

The three processes for carboxylic acids are the above two plus the following:

Hancock, Gilby and Westmoreland[22] argued in favor of equation (9) on the grounds that the more positive of the two oxygens, that is, the O-H oxygen, is more likely to attack the nucleophilic diazo carbon. There is, however, no evidence for favoring any of the three modes of proton transfer. Any arguments advanced are mere speculation.

Diazonium Ion Intermediate. If the reaction proceeds through a single step process, that is, a reversible hydrogen bonding between the acidic hydrogen of the general acid and the DDM followed by a rate determining reaction of the complex, then the ester:ether ratio should be a function of per cent dissociation of the acid involved.

Since it has been found that a large number of acids with varying acid strengths give essentially the same product ratios (Table III), the single step mechanism is probably not correct. The other alternative is, of course, the diazonium ion intermediate.

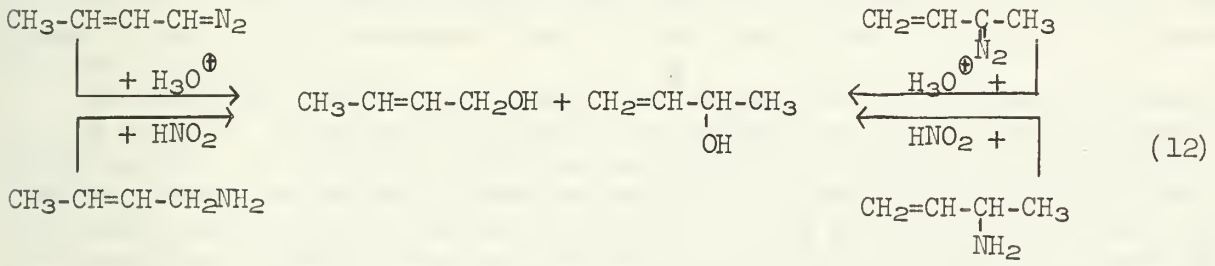
Whether the acid catalyzed decomposition of diazo compounds proceeds through diazonium ion intermediates or not is still held to be controversial. Nevertheless, there are some very convincing evidence to indicate that it is a reasonable postulate. Huisgen and Rüchardt[23] have demonstrated that the amount of isopropyl alcohol formed from the deamination of n-propylamine and the decomposition of n-diazopropane is about the same (Table II).

Table II

Decomposition of n-propyldiazonium ion in aqueous dimethylforamide

System	Temp.	% Isopropanol
n-propylamine + $HClO_4$ + $NaNO_2$	0°	30.8
n-diazopropane + $HClO_4$	0°	28.1
n-diazopropane + benzoic acid	0°	27.2

Further evidence of diazonium ion intermediacy was demonstrated by Curtin and Gerber,[24] and Roberts and Mazur.[25] Curtin and Gerber found that the reaction of 1-diazo-2-butene and 3-diazo-1-butene in aqueous perchloric acid gives approximately the same relative amounts of 3-butene-1-ol and 2-butene-1-ol. The same relative yields of 3-butene-1-ol and 2-butene-1-ol were obtained by Roberts and Mazur for the deamination of 1-amino-2-butene and 2-amino-1-butene (Eq. 12).

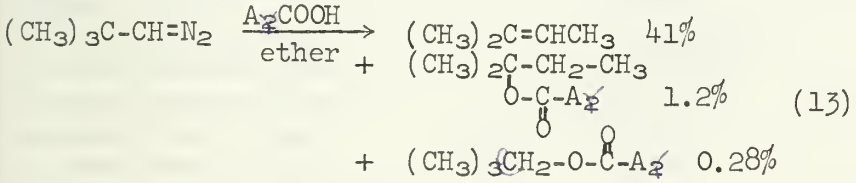


(12)

A further indication that the reaction proceeds through an intermediate of high ionic character is provided by Taft and Smith.[3] They found that the reaction of DDM with RCOOH in absolute ethanol at 25° where R is a relatively small group ($C_6H_5CH_2$- group included) has a $\rho^* = +1.18$. For 4-X-bicyclo [2.2.2.] octane-1-carboxylic acids, X--CO_2H, the $\rho^* = +4.16$. Roberts and coworkers[4] also found a $\rho = +0.937$ for substituted benzoic acids under the same conditions.

It can therefore be said with reasonable certainty that the acid catalyzed decomposition of DDM in ethanol proceeds via a diazonium ion intermediate.

Consequences of Diazonium Ion Intermediate. It is generally assumed that the decomposition of diazonium ions proceeds through a mechanism of S_N1 or carbonium ion character.[6] Curtin and Gerber[24] provided very compelling evidence for the validity of this assumption. They found that diazoneopentane reacts with 3,5-dinitro-benzoic acid in ether to give trimethylethylene as the major product. There is only 0.28% of the unrearranged product (Eq. 13). The products are stable under reaction conditions.



(13)

The methyl migration provides good evidence for carbonium ion character.

The demonstration of carbonium ion character notwithstanding, the decomposition of diazonium ions gives somewhat different product ratios than the solvolysis of corresponding halide. A very striking example of this is provided by Roberts.[12] As mentioned earlier, he found that the reaction of DDM with benzoic acid in ethanol gives 60% ester and 40% ether. Under completely analogous conditions, the ethanolysis of benzhydryl chloride in the presence of benzoate ions gives almost no ester.

Huisgen and Reimlinger[26] pointed out that formation of a carbonium ion from alkyldiazonium ion is exothermic whereas the same for alkyl halides are highly

endothermic. Assuming the starting materials to have the same energy, the following energy profile could be drawn (Fig. 2).[23] The activation energies for the formation

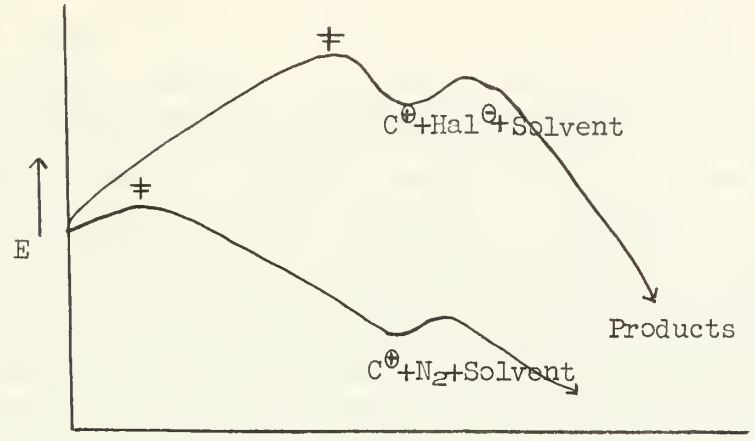


Fig. 2

Energy profile of the solvolyses of alkyl halide and alkyldiazonium ion.

of carbonium ion from diazonium ion and alkyl halide has been estimated to be about 5 kcal./mole and 25 kcal./mole, respectively.[9] The exothermicity in the carbonium ion formation from alkyldiazonium ions gives the carbonium ion an excess energy sometimes called a "hot" carbonium ion. Herein lies perhaps the major difference between the two carbonium ions.

Streitwieser[27] correctly pointed out an important consequence to the proposed energy profile. Consider a system of competing reactions in the solvolysis of an alkyl halide. If the solvolysis has an activation energy of 25 kcal./mole, and the competing reaction has an activation energy of 30 kcal./mole or 5 kcal./mole higher, the competing reaction would have a yield of 0.02% at room temperature. In the corresponding diazonium ion reaction, if the activation energy is 5 kcal./mole, the same competing reaction would be expected to have a proportionately higher energy, or 6 kcal./mole. In this case the yield for the competing reaction would be 16%. If this argument were invoked, it is possible to qualitatively, though not quantitatively, explain the tremendous difference in the yields of benzhydryl chloride and DDM.

The exothermicity of carbonium ion formation from the diazonium ion obtained from DDM has another important consequence. According to the Hammond Principle,[28] the transition state for the decomposition of the diazonium ion would resemble the reactants. Accordingly if there is an attacking particle, the bond of the diazonium ion to the attacking particle is long and weak in the transition state. Hence steric effects would be minimized. To put it differently, the carbonium ion, having an excess energy, is unselective. This is borne out by experiment as shown in Table III.

Table III

Values for the reaction DDM + HA $\xrightarrow{\text{EtOH}}$ ester + ether.

Acid	Temp.	% ester	Ref.
Benzoic Acid	30°	60.0	12
p-Nitrobenzoic Acid	30°,25.9°	57.6,65.0	17,16
p-Methoxybenzoic Acid	30°,25.9°	60.0,66.0	17,16
o-Fluorobenzoic Acid	30°	61.0	5
o-Aminobenzoic Acid	30°	60.0	17
o-tButylbenzoic Acid	30°	65.8	5
2,6-Dichlorobenzoic Acid	30°	64.0	19
cis and trans-1,2-Cyclohexane-dicarboxylic Acid	25°	60.0	18
cis and trans-1,4-Cyclohexane-dicarboxylic Acid	25°	60.0	18
2-Naphthoic Acid	30°	58.6	17
2-Anthroic Acid	30°	59.0	17
Biphenyl-4-carboxylic Acid	30°	58.3	17
Formic Acid	25.9°	81.0	16

Acid	Temp.	% ester	Ref.
2,6-Dinitrophenol	25.9°	68.0	16
Picric Acid	30°	0.0	11
p-Toluenesulfonic Acid	30°	0.0	11

Parallel Reaction Paths. Roberts' experiments on the effect of dissociation of picric acid on the rate of reaction between DDM and picric acid, and the effect of water and benzoate ion on the rate of the reaction between DDM and benzoic acid discussed earlier can also be taken to argue for parallel reaction paths. It was pointed out that the acid as well as the ethyloxonium ion catalyzed the reaction.

The reaction of DDM with 2,4-dinitrophenol in ethanol is first order in DDM and first order in 2,4-dinitrophenol or second order overall.[13] The reaction products are 61% benzhydryl-2,4-dinitrophenyl ether and 39% benzhydryl ethyl ether. However, at ionic strength of 0.1, and using lithium perchlorate as the inert salt, the reaction rate was increased by 40% and the benzhydryl ethyl ether yield increased from 39% to 57%. It was further noticed that at ionic strength of 0.1, addition of 2,4-dinitrophenoxide ion sharply decreases the rate as was the case for benzoic acid (Fig. 1). Finally the amount of benzhydryl ethyl ether formed is sharply reduced by the addition of 2,4-dinitrophenoxide ions, and at 0.1M lithium 2,4-dinitrophenoxide concentration, the amount of benzhydryl ethyl ether formed is 34%, about the same as in the absence of an added salt. It is significant to point out that the reduction in the formation of benzhydryl ethyl ether (23%) is in good agreement with the value (24%) calculated from the concomitant reduction in the overall reaction rate base on the assumption that the ethyloxonium ion catalyzed reaction yields only benzhydryl ethyl ether.

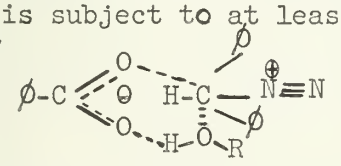
All these results can be rationalized by parallel reaction paths. The added salt would increase the degree of dissociation of the phenol, resulting in an increase in the concentration of the ethyloxonium ion and hence an increase in the rate and the amount of benzhydryl ethyl ether. Addition of 2,4-dinitrophenoxide ion suppresses the degree of dissociation according to the Law of Mass Action, and hence decreases the rate and the amount of benzhydryl ethyl ether formed.

Common Intermediate. Parallel reaction paths, however, cannot explain the high per cent yield of benzhydryl benzoate in the reaction of DDM with benzoic acid even by invoking the low activation energy for the decomposition of diazonium ions. In general, it cannot explain the constancy of the ester:ether ratio (Table III).

Moreover, it was found that α, the per cent ester yield, is independent of temperature. A change of 50° in temperature causes a change of less than 1% in α for benzoic acid while the rate is increased by a factor of 50 for the same rise in temperature.[17] If the reaction proceeds by parallel reaction paths, it would require that both paths have very similar activation energies which does not seem to be the case on the basis of Roberts' findings that ethyloxonium ion reacts much faster with DDM than benzoic acid.

Miller and coworkers[16] suggested a common ion pair intermediate (Eq. 6) where the amount of ester or ether formed depends on the relative tendencies of the ion pair to collapse or dissociate, respectively. This would perhaps explain the constancy of ester:ether ratio, but it seems to disregard the ethyloxonium ion catalysis demonstrated by Roberts.

Chapman and coworkers[17] proposed yet another variation. They proposed a common intermediate with a structure like (I). It is in effect more or less an ion pair and is subject to at least the same criticism given Miller's ion pair proposal.



(I)

Conclusion. It is obvious that neither the parallel reaction paths mechanism, that is, the mechanism involving catalysis by both the acid HA and the ethyloxonium ion, nor the common intermediate mechanism which involves the common ion pair $(C_6H_5)_2-CH^{\oplus}A^{\ominus}$, would adequately explain all the experimental observations. However, if both mechanisms are operative, most of the experimental observations could be explained.

It is possible that most acids are not highly dissociated in ethanol since it does not have a high ionizing power. There might exist a precarious, though fortuitous, balance between the extent of ionization and the per cent ion pair return. The special features of the diazonium ion reaction making competing side reactions more favorable should, of course, also be taken into consideration. In the case of a very strong acid, or increase of dissociation to a significant degree by addition of salts or water, there is no longer a balance and the constancy of ester:ether ratio is upset. Although this explanation may not be very satisfactory, it is probably the best available.

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THE STRUCTURE OF TETRODOTOXIN

Reported by Thomas Sharpe May 6, 1965

INTRODUCTION.- Puffer fish poisoning has long been a problem in Japan. About two hundred people die annually from the effects of this poison.[1] The toxin, known today as tetrodotoxin, was first isolated in pure, crystalline form by Yokoo[2] in 1950 from the ovaries of the tiger puffer, Sphoeroides rubripes. Aside from certain toxic protein materials, tetrodotoxin is one of the most toxic compounds known.[3] It is the purpose of this seminar to review the chemical investigations which have led to the elucidation of the structure of tetrodotoxin.

PHYSICAL PROPERTIES AND MOLECULAR FORMULA. - Tetrodotoxin (I), colorless prisms from dilute acetic acid, decomposes without melting around 220°. It is insoluble in water but soluble in dilute acid and is a weakly basic substance with a pK_a of 8.3 (in water). The toxin shows only end absorption in the UV, and the IR shows absorptions at 1660 and 1600 cm^{-1}.[4]

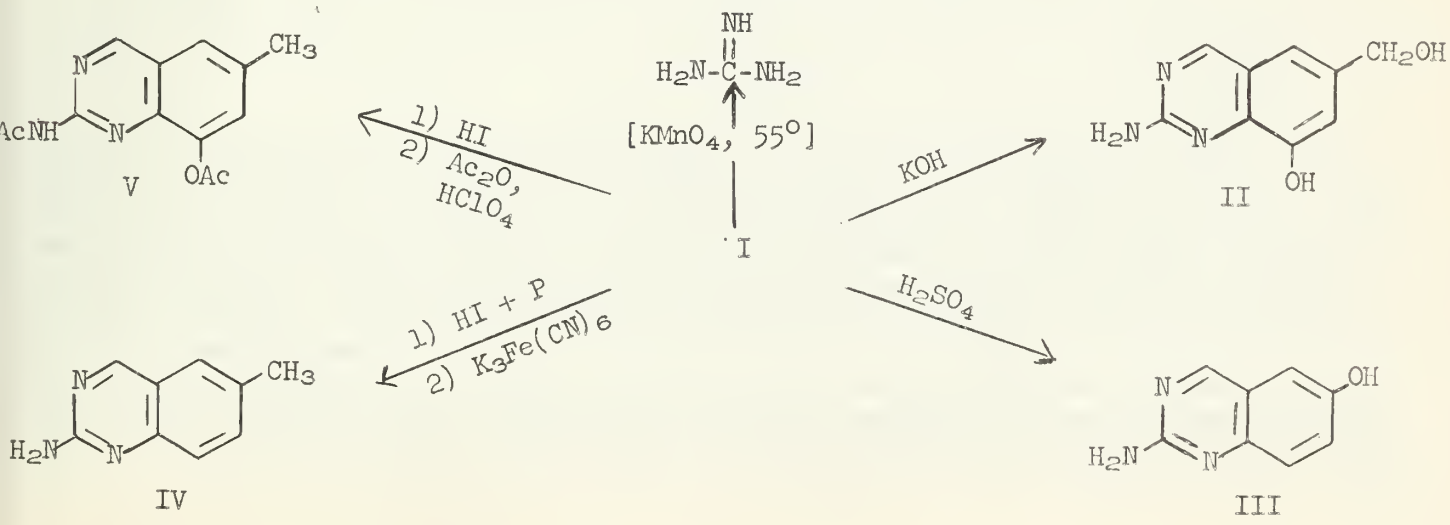
Early work directed toward establishing the molecular formula of tetrodotoxin gave conflicting results. Yokoo[5] first proposed $C_{12}H_{17}O_{10}N_3$ for the toxin, while Kakisawa and co-workers,[6] on the basis of analytical data and titration results, favored $C_{12}H_{19}O_9N_3$. Tsuda was originally in agreement with the latter formula,[7] but he later revised it to $C_{11}H_{17}O_8N_3$.[8] The latter, currently accepted formula was also established by Goto and co-workers[9] from analytical results and by Woodward[10] on the basis of a mass spectrometric investigation of a mixture of peracetyltetrodotoxins. The early conflicting analytical data probably arose from varying amounts of hydroxylic solvents or water absorbed by the toxin as a consequence of its highly polar nature. Much of the structural work was carried out without exact knowledge of the formula of the toxin.

STRUCTURAL INVESTIGATIONS. - Goto and co-workers[4] and the Woodward group[10] reported the isolation of guanidine in the form of its picrate when tetrodotoxin was subjected to permanganate oxidation. From this it was concluded that the three nitrogen atoms present in the toxin existed in the form of an intact guanidine unit.

Tetrodotoxin was degraded under both basic and acidic conditions. When tetrodotoxin was heated in the presence of alkali a C_9-base was obtained,[11] which was identified as 2-amino-6-hydroxymethyl-8-hydroxyquinazoline (II) by chemical and physical methods.[12,13] Tsuda also established the structure by synthesis of the C_8 methyl ether of II.[14] Oxalic acid was also isolated from this reaction. Treatment of tetrodotoxin with concentrated sulfuric acid afforded 2-amino-6-hydroxyquinazoline (III), whose structure was established by analysis, UV and NMR.[15]

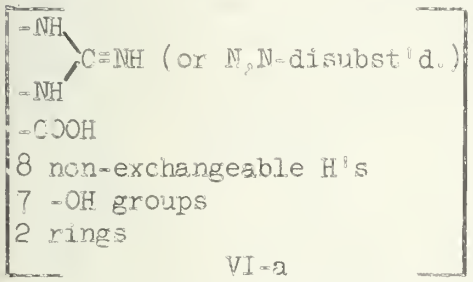
Yet another quinazoline was obtained when tetrodotoxin was heated with hydrogen iodide and red phosphorus followed by oxidation with potassium ferricyanide. This product was shown to be 2-amino-6-methylquinazoline (IV).[16] A similar reductive degradation afforded Woodward 2-acetylamino-6-methyl-8-acetoxyquinazoline (V).[10]

These degradative transformations are summarized below:



The formation of these various quinazolines in good yield under a variety of both acidic and basic conditions suggested that the perhydroquinazoline ring system was the basic ring system for the tetrodotoxin molecule.

The first derivative of tetrodotoxin that contained all eleven carbon atoms was obtained by Tsuda and co-workers[17] and the Goto group[4] when tetrodotoxin was refluxed with water. The crystalline substance (VI) so obtained was formulated as $C_{11}H_{19}O_9N_3$ by both groups and was called tetrodonic acid by Tsuda and tetrodoic acid by Goto. The latter name will be used in this abstract when referring to VI. Tetrodoic acid shows only end absorption in the UV and in the IR absorbs at 1690 and 1576 $cm.^{-1}$ (disubstituted guanidine[18]) and 1594 and 1416 $cm.^{-1}$ (carboxylate anion). VI was found to be zwitterionic with pK_a's 11.9 (guanidine) and 2.9 (carboxyl). The guanidine group was also shown to be present from the production of guanidine in the permanganate oxidation of VI.[19] VI does not absorb bromine and shows a negative Sakaguchi test (not a monosubstituted guanidine). The NMR of VI hydrochloride in D_2O (see figure 1) showed signals corresponding to eight hydrogens that did not exchange with deuterium.[4] From the molecular formula of VI and the above results it was concluded that tetrodoic acid contains a disubstituted guanidine group, seven hydroxyl groups and two rings. The number of non-exchangeable hydrogen atoms would exceed eight if there were present oxygen atoms other than hydroxyl and/or a tri- or more substituted guanidine group. A partial structure of VI was then represented by VI-a.

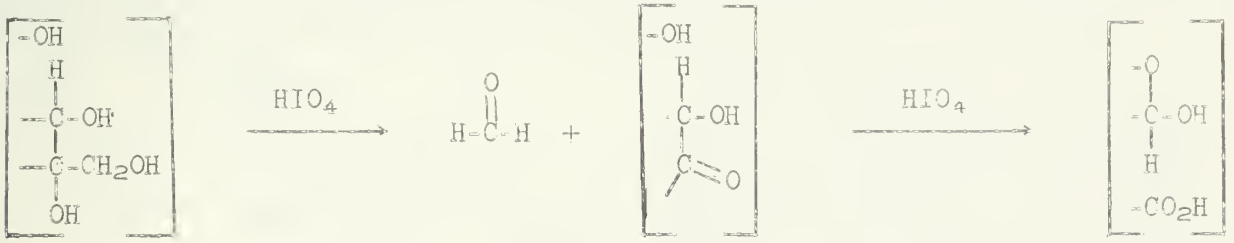


VI-a

Tetrodoic acid reacted with HIO_4 at 0° and produced formaldehyde and nortetrodoic acid (VII) after the first mole of HIO_4 was consumed.[4] VII, formulated as $C_{10}H_{15}O_8N_3 \cdot 1/2\ H_2O$, shows pK_a's 3(CO_2H) and 11 (guanidine). VII has IR absorptions at 1690 cm^{-1} (C=O), 1670 and 1645 cm^{-1} (disubstituted guanidine) and 1612 cm^{-1} (carboxylate anion). VII consumed one mole of HIO_4 in 0.1 N H_2SO_4 at 4° and produced seconortetrododioc acid (VIII).

Seconortetrododioc acid (VIII), $C_{10}H_{15}O_9N_3$, has pK_a's below 2 (CO_2H), 3.3 (CO_2H) and above 10.5 (guanidine). VIII shows IR absorptions at 1750 cm^{-1} (CO_2H), 1675 and 1640 cm^{-1} (disubstituted guanidine) and 1600 cm^{-1} (carboxylate). VIII consumed no HIO_4 in 0.1 N H_2SO_4 after 24 hours.

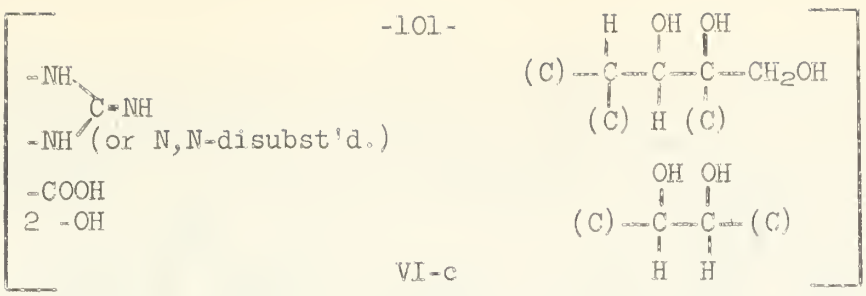
The NMR spectrum of VII showed a doublet in the region 2.0-2.5 ppm. (ppm upfield from external benzene) which was absent in VIII. However, a new doublet appeared in VIII at 1.5 ppm. This doublet in VIII was assumed to be due to a proton attached to a hemiacetal carbon atom which was produced in the HIO_4 oxidation of a secondary alcohol. The conversion of VI to VIII was represented by the following sequence.



VI-b VII-b VIII-b

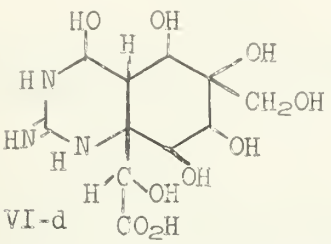
It was also shown that the hemiacetal proton in VIII was coupled to a proton which appeared in the NMR at 3.75 ppm, and it was assumed from the high-field resonance that this latter proton was attached to a carbon atom bearing only other carbon atoms. The NMR spectrum of VI showed a pair of doublets at 2.05 and 2.45 ppm. with a coupling constant of 4 cps. These resonances were assumed to be due to a vicinal di-secondary alcohol grouping. From these observations the partial structure VI-c of tetrodoic acid (VI) was proposed.

When tetrodoic acid (VI) was heated with base, the same C_9-base was obtained that was formed when tetrodotoxin was subjected to the same conditions, namely 2-amino-6-hydroxymethyl-8-hydroxyquinazoline (II). Thus if one accepts the perhydroquinazoline ring

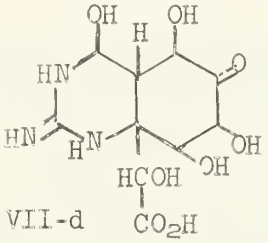


VI-c

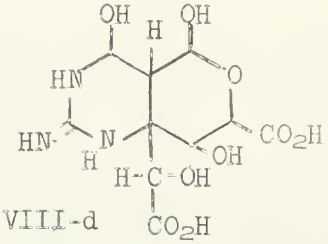
system as the basic skeleton for tetrodoic acid (VI), and if the hydroxymethyl group is placed at the C_6 position (corresponding to its location in II) the formula for tetrodoic acid that best accomodates the available data is VI-d. Nortetrodoic acid (VII) and seconortetrododioc acid (VIII) would then be VII-d and VIII-d respectively.



VI-d

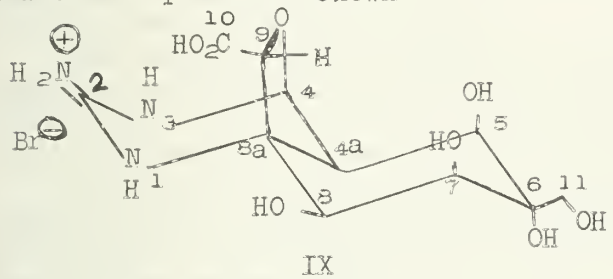


VII-d



VIII-d

When tetrodoic acid (VI) was treated with hydrobromic acid, tetrodoic acid hydrobromide (IX) was obtained which was shown to have formula $C_{11}H_{17}O_8N_3 \cdot HBr$.[17] IX shows IR absorption at 1724 cm^{-1} (CO_2H) and 1665 and 1576 cm^{-1} (disubstituted guanidine). X-ray crystallographic studies were carried out on tetrodoic acid hydrobromide (IX) and the compound was shown to have the structure as shown:



IX

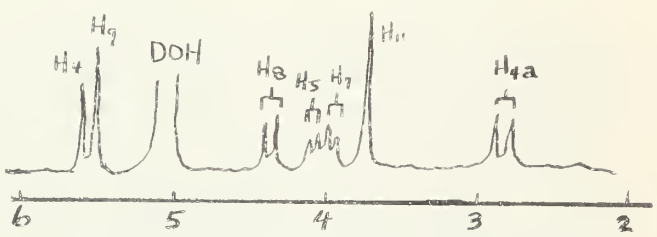
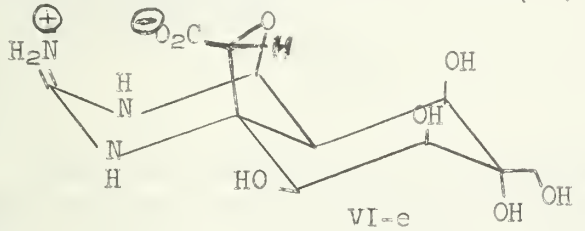


Fig. 1: Tetrodoic Acid (D_2O-H_2SO_4) p.p.m. from external TMS

This structure for IX is also supported by the NMR spectrum of VI taken in acid solution (see figure 1).[19]

When tetrodoic acid (VI) was heated *in vacuo* at 100° for thirty hours it was converted into a crystalline substance with the formula $C_{11}H_{17}O_8N_3$.[8] This latter compound could be reconverted to VI on treatment with water at room temperature. From this it was concluded that tetrodoic acid (VI) should be represented as a hydrate of VI-e rather than by formula VI-d.



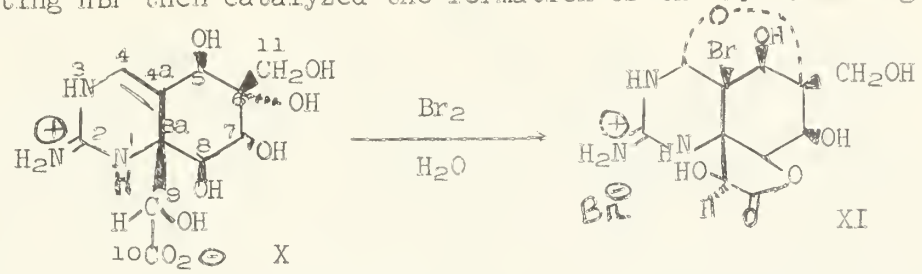
VI-e

When tetrodotoxin was treated with 5 % $Ba(OH)_2$ at room temperature another crystalline C_{11}-derivative was obtained in almost quantitative yield.[20] This compound was called anhydrotetrodoic acid (X) and was assigned the formula $C_{11}H_{17}O_8N_3 \cdot 2\ 1/2\ H_2O$.

X exhibits the following UV properties: $\lambda_{max}^{H_2O}$ 261 mμ (ε 5930), $\lambda_{max}^{0.1N\ NaOH}$ 290 (ε 6420), $\lambda_{max}^{0.1N\ HCl}$ 257 (ε 6050). X shows IR absorptions at 1710 cm^{-1} (guanidine) and 1580 cm^{-1} (carboxylate anion). The pK_a values of X were found to be 2.5 (CO_2H) and 10.9 (guanidine).

X consumed one mole of bromine in water and produced bromoanhydrotetrodoic lactone hydrobromide (XI). The empirical formula of XI was found to be $C_{11}H_{15}O_7N_3Br_2$. XI shows only end absorption in the UV and absorbs in the IR at 1800 cm^{-1} (γ-lactone) and 1665 and 1608 cm^{-1} (disubstituted guanidine). XI was found to be stable in acids but quite unstable in base. The γ-lactone ring could be opened by neutralization to pH 7.5 as evidenced by the disappearance of the 1800 cm^{-1} band and appearance of a new band at 1605 cm^{-1} (presumably due to CO_2^-). XI was subjected to X-ray crystallographic

analysis and was shown to have the structure as shown.[21] The structure for anhydrotetrodoic acid (X) could then also be assigned. The formation of XI from X involved the attack of bromonium ion at C_{4a} with ether formation between the C_4 and C_6-hydroxyl groups. The resulting HBr then catalyzed the formation of the lactone ring.



X XI

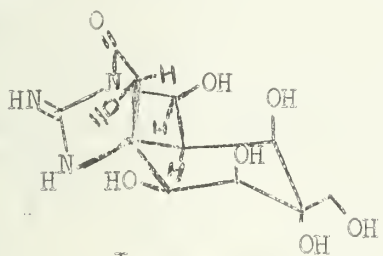
It can be seen that the configuration at C_9 in tetrodoic acid (VI-e) is opposite to that in bromoanhydrotetrodoic lactone hydrobromide (XI).

$$\text{XI} \xleftarrow[(C)]{Br_2(H_2O)} \text{X} \xleftarrow[(A)]{Ba(OH)_2} \text{I} \xrightarrow[(B)]{H_2O} \text{VI-e}$$

Goto and co-workers[22] found that when tetrodoic acid (VI-e) was prepared from tetrodotoxin using deuterium oxide, exchange of deuterium for hydrogen had occurred at C_9. When reaction A was carried out using $Ba(OD)_2$ in deuterium oxide, no carbon-hydrogen bonds exchanged with the deuterium. This suggested the possibility that epimerization had occurred during reaction B. However, exchange could have occurred during reaction B without epimerization, and inversion at C_9 could have taken place during reaction C. This latter possibility can not be ruled out, since reaction C was not carried out using deuterium oxide as solvent.

The problem of determining the structure of tetrodotoxin now consisted in finding that structure which could revert to compounds VI-e and X under the conditions described above and is compatible with the existing physical data, namely, the lack of UV absorption, the absence of bands in the IR between 1700-1800 cm^{-1}, and the pK_a value of 8.3.

The free carboxyl group in VI-e and X is not present in tetrodotoxin, and the pK_a value of 8.3 is clearly too low to be associated with a guanidinium system whose values are usually in the range 10-14.[23] One possible way to reduce the basicity of the guanidinium system and dispose of the unwanted CO_2H group would be through acylation, and one of the first structures considered for tetrodotoxin with this idea in mind was I-a.[7,20]



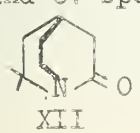
I-a

Fig. 2: Tetrodotoxin (CD_3CO_2D-D_2O) p.p.m. from external TMS

The configuration at C_4 was assigned as follows: the high field resonance in the NMR spectrum of tetrodoic acid (see figure 1) assigned to the C_{4a}-proton is also present in tetrodotoxin (see figure 2), but in tetrodotoxin the C_{4a}-proton is coupled to the C_4-proton (low field resonance) with a coupling constant of 10 cps which suggests a dihedral angle close to 0° or 180°.

Goto and co-workers[20] assumed that the carbonyl band in I-a overlapped with the guanidine band at 1660 $cm.^{-1}$, and they stated that an amorphous sulfate of tetrodotoxin does indeed show a band in the IR at 1730 $cm.^{-1}$.

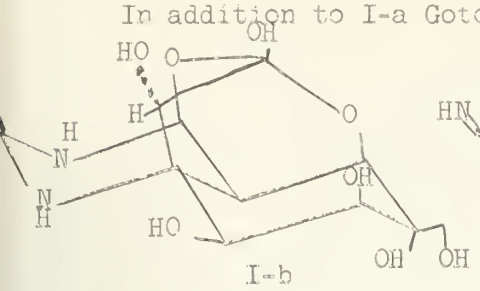
Mosher[3] has criticized the bridgehead amide structure I-a on the basis of the IR and UV spectra of tetrodotoxin. Although compounds containing a bridgehead amide structure are rare, known cases show spectral properties quite different from those of tetrodotoxin. Pracejus[24] reports that 6,6-dimethylquinuclidone (XII) shows IR absorption at 1735 $cm.^{-1}$ while tetrodo-



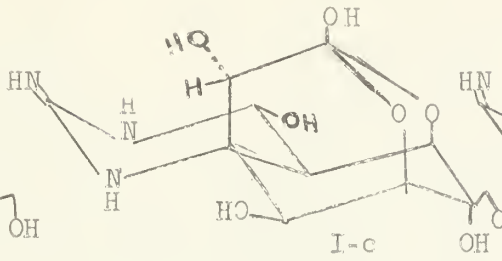
XII

toxin absorbs at 1660 cm.$^{-1}$. Also XII absorbs in the UV at 246 mμ (ε 120) while tetrodotoxin is transparent in the UV.

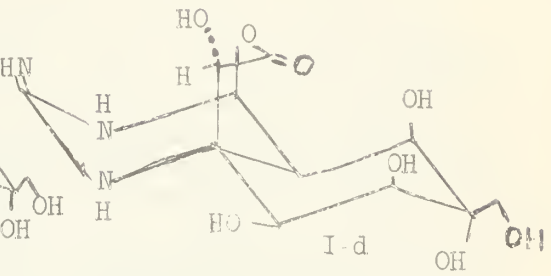
In addition to I-a Goto also considered structures I-b, I-c, and I-d:[20]



I-b



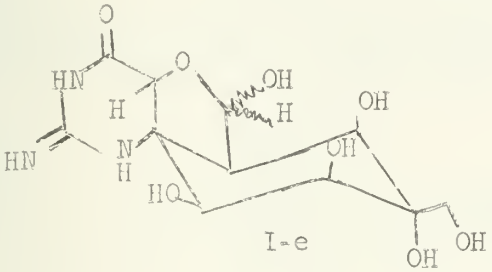
I-c



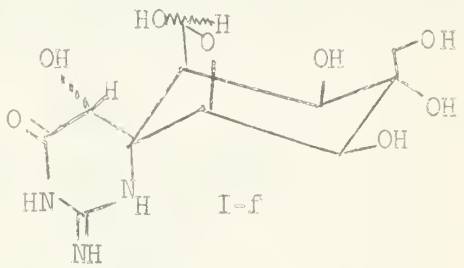
I-d

The lactone form I-d was ruled out since tetrodotoxin shows no IR absorption between 1700-1800 cm.$^{-1}$. The ortho ester formulas I-b and I-c were ruled out since they could not account for the low basicity of the toxin. Also, structure I-b is inconsistent with the 10 cps. coupling constant found for the C_4- and C_{4a}-protons.

Tsuda[17] had earlier proposed I-a as a structure for tetrodotoxin (with the configuration at C_9 inverted and the C_4-configuration undesignated) as well as the spirane-type structures I-e and I-f. These two forms are not bridgehead amide structures, and



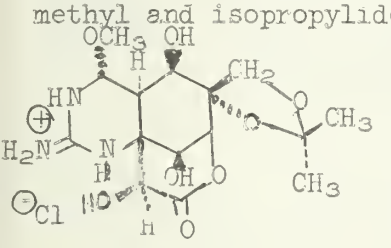
I-e



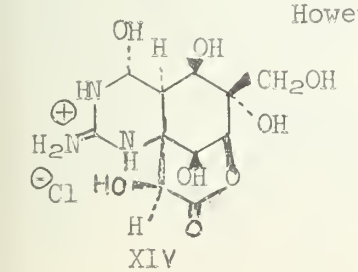
I-f

therefore they are not subject to the same type of criticism Mosher had for I-a. However, Tsuda[8,19] later abandoned such lactam formulas from the results of the periodic acid oxidation experiments discussed below. Also, these structures do not contain the perhydroquinazoline ring system which was thought to be present in tetrodotoxin from the many quinazolines obtained as degradation products.

At this same time completely independent work on the structure of tetrodotoxin was being carried out by the Woodward group.[10] This group had found that treatment of tetrodotoxin in an acetone-methanol solution with anhydrous hydrogen chloride gave a crystalline derivative which turned out to be O-methyl-O^{1},O^{11}-isopropylidenetetrodotoxin hydrochloride (XIII). Except for the resonances associated with the added methyl and isopropylidene groups the NMR spectrum of XIII was almost superimposable with that of tetrodotoxin dissolved in dilute acid. From this it was concluded that XIII was formed from tetrodotoxin with very little structural change. While the NMR spectrum of tetrodotoxin dissolved in mineral acid was not definitive, the NMR spectrum of XIII in D_2O showed clearly the presence of eight carbon-hydrogen bonds. An X-ray crystallographic analysis of XIII afforded the structure shown. Both XIII and tetrodotoxin hydrochloride (XIV) show bands in the IR at 1750 cm.$^{-1}$, and it was concluded that XIV possesses the structure shown



XIII

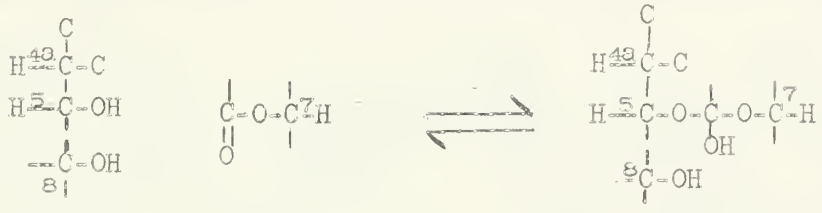


XIV

However, the fact that tetrodotoxin itself was not merely the deprotonated analog of XIV was obvious from the following considerations: (1) Tetrodotoxin does not possess a lactone system. The 1750 cm.$^{-1}$ band present in the IR spectra of XIII and XIV is absent in the IR spectrum of tetrodotoxin (2) As stated previously the pK_a of tetrodotoxin is much too low to be associated with a guandinium system. (3) The two bands at 1660 and 1600 cm.$^{-1}$ present in the IR spectra of XIII and XIV assignable to the guanidine system appeared unchanged in the

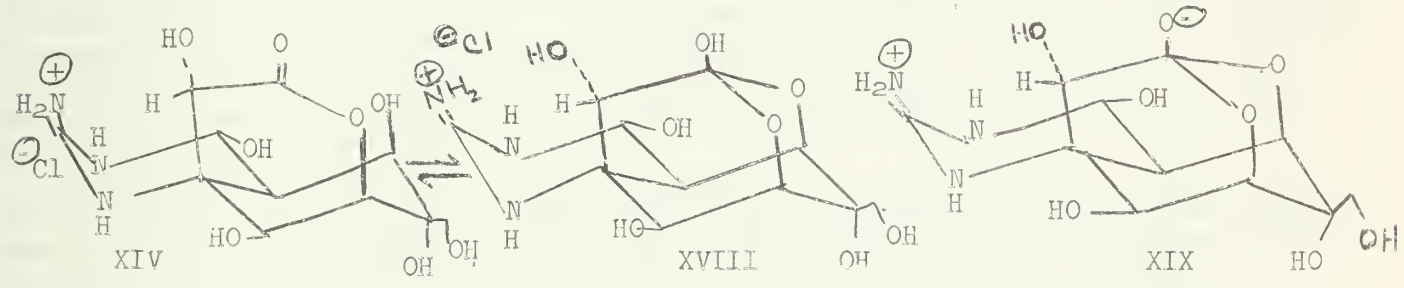
free base of XIII and tetrodotoxin From this latter observation it was concluded that the deprotonation of the salts XIII and XIV occurs from some site other than the guanidinium group. Evidence for this was obtained from measurements of the pK_a of XIII in solvent systems other than pure water. For example, the pK_a of XIII in water was found to be 8.3 while in 70% aqueous dioxane a value of 9.2 was obtained. This increase in pK_a with decrease in dielectric constant was evidence that dissociation occurs from a hydroxyl group rather than from the positively charged guanidinium group.[25] This result indicated that tetrodotoxin and the free base of XIII are zwitterions. The problem now was to determine from which hydroxyl group dissociation was occurring, and it was not immediately apparent why any of the hydroxyl groups should be associated with the fairly acidic pK_a of 8.3.

This problem was solved from a consideration of the NMR spectrum of heptaacetylanhydrotetrodotoxin (XV). This compound was prepared by the acetylation of tetrodotoxin with acetic anhydride in the presence of pyridine and was shown to have the formula $C_{25}H_{29}O_{14}N_3$ by analysis and mass spectrometry. If the molecule XIV were acetylated three HC(C,C,OAc) groups should result (at C_5, C_7 and C_8). However, the NMR spectrum of XV showed only one such group. The resonance of this type of hydrogen in the NMR spectrum should occur at a lower field than the resonance of the $H_2C(C,OAc)$ group which was found at τ 5.01. In the NMR spectrum of XV only two signals were found below τ 5.01; the low field resonance (sharp singlet) at τ 3.89 was assigned to the HC(C,O,N) proton while the other at τ 4.60 (doublet, J=1.8 cps.) was assigned to the HC(C,C,OAc) proton. This indicated to the Woodward group that two of the groups shown in XVI should combine to form a new system as shown in XVII:



XVI XVII

Double resonance experiments showed that it is the C_5-hydroxyl group that combines with the lactone group to form the hemilactal system shown in XVII. Woodward points out that the band at 1750 $cm.^{-1}$ in the IR spectrum of amorphous tetrodotoxin hydrochloride XIV) is relatively weak, and he concludes that in this material both forms XIV and XVIII exist. The free base tetrodotoxin was then assigned the zwitterionic,

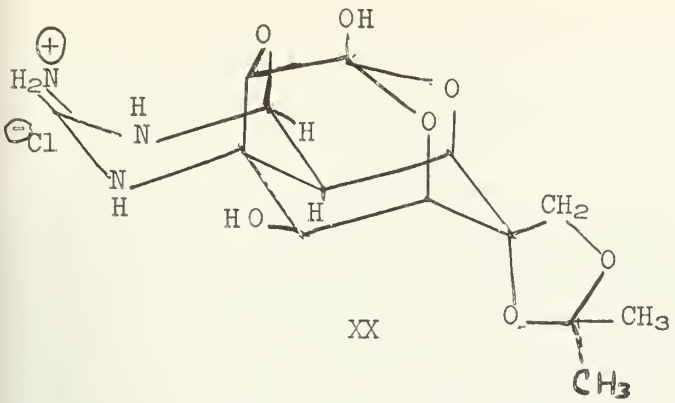


XIV XVIII XIX

dioxoadamantane structure XIX.

The crystalline O-methyl-O',O''-isopropylidenetetrodotoxin hydrochloride (XIII) exists entirely in the lactone form, but this form could be equilibrated with the hemilactal form in solution. For example, it was estimated from the IR spectrum that about 70% of the molecules of XIII exist in the hemilactal form when dissolved in DMSO, while in D_2O it was estimated that about 90% of the molecules exist as the hemilactal.

When tetrodotoxin was treated with hydrogen chloride in acetone there was obtained crystalline O,O'-isopropylideneanhydrotetrodotoxin hydrochloride (XX). This compound was shown to exist completely in the hemilactal form as the solid and in several different solvents. Several different derivatives of tetrodotoxin belonging to this anhydro series (i.e., derivatives with the C_9-O-C_4 ether bridge) have been prepared, and their NMR spectra are quite characteristic. The high field C_{4a}-proton resonance

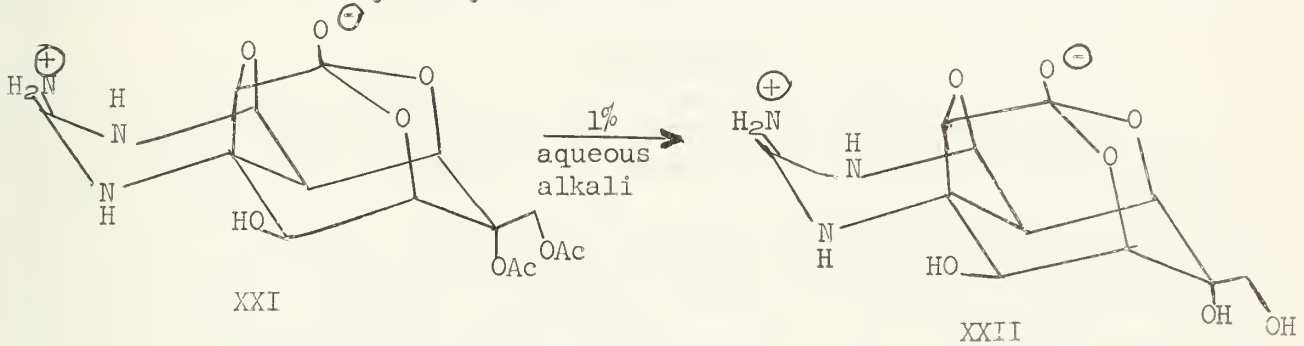


XX

appears as a doublet (J=3 cps.) and the low field C_4-proton resonance appears as a sharp singlet. The inversion of configuration at C_4 and the C_9-O-C_4 bridge results in a dihedral angle of about 90° for the C_4-H, C_{4a}-H bonds which reduces the coupling constant to near zero.

As stated previously Goto had ruled out the hemilactal form I-c as a possible structure for tetrodotoxin on grounds that it would not account for the low basicity of the toxin.[22] However, he later observed the same increase in pK_a with decrease in dielectric constant as Woodward noted.[22] For example, he found the pKa of tetrodotoxin in 50% aqueous ethanol to be 9.4, and he stated that the C_{10}-hydroxyl group of I-c could account for this property. In a later paper[26] Goto presented the zwitterionic structure XIX for the toxin.

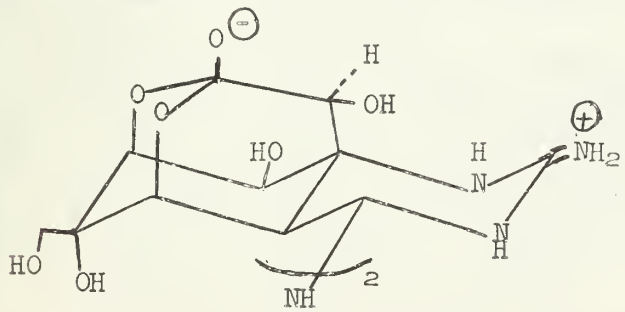
Tsuda and co-workers observed this same dependence of pKa on solvent and they arrived at structure XIX independently.[8,19] They found that treatment of tetrodotoxin with acetic anhydride and pyridine gave a polyacetate which on treatment with methanol gave a crystalline diacetate with the formula $C_{15}H_{19}O_9N_3$.[8] This compound proved to be 6,11-diacetylanhydrotetrodotoxin (XXI) whose structure was assigned on the basis of NMR and X-ray analysis. Treatment of XXI with dilute alkali afforded



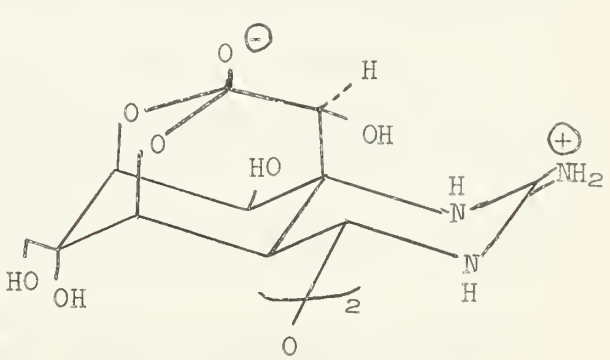
XXI XXII

anhydrotetrodotoxin (XXII). While tetrodotoxin consumes three moles of periodic acid in eight hours at 3°, anhydrotetrodotoxin (XXII) requires about three days to consume the second mole of HIO_4.[19] This slower consumption of HIO_4 by XXII is understandable if the equilibrium between the lactone form and the hemilactal form lies strongly in favor of the latter in XXII. This same effect could explain the observation[22] that anhydrotetrodotoxin (XXII) is quite stable to base while tetrodotoxin is unstable above pH 9.

When anhydrotetrodotoxin (XXII) was treated with excess aqueous ammonia there was obtained tetrodaminotoxin (XXIII).[8,22] Tsuda obtained better analytical results based on the formula $C_{22}H_{33}O_{14}N_7$ for XXIII than on $C_{11}H_{18}O_7N_4$, and he suggested that XXIII could have been formed from one mole of NH_3 and two moles of XXII.[27] Since the NMR, IR, and X-ray powder diffraction data were very similar for tetrodotoxin



XXIII



XXIV

and XXIII, Tsuda suggested that tetrodotoxin could have structure XXIV. Tetrodotoxin is only soluble in acid solutions, and lability of the ether linkage in XXIV in these solutions could account for the observation that all transformation products of tetrodotoxin derive from the C_{11}-formula(XIX). However, Woodward and Gougoutas[28] ruled out structure XXIV for crystalline tetrodotoxin by showing that the cell weight obtained from X-ray crystallography is incompatible with structure XXIV while in complete agreement with XIX.

TARICHATOXIN: IDENTITY WITH TETRODOTOXIN. - In 1961 H. S. Mosher and co-workers at Stanford began working on the toxic principle present in the embryos of the California salamander, Taricha torosa. After this toxin, known as tarichatoxin, was isolated in pure, crystalline form the Stanford group assigned to it the formula $C_{11}H_{17}O_8N_3 \cdot 1/2\ H_2O$. After having become aware of the remarkable similarity in chemical and pharmacological properties of tetrodotoxin and tarichatoxin, Mosher obtained a sample of tetrodotoxin from the Japanese group headed by Tsuda and set out to make direct comparisons of the two toxins and their derivatives.

Diacetate, pentaacetate, and heptaacetate derivatives of the two toxins showed identical melting points, mass spectra, IR and NMR spectra and optical rotations.[3,29,30] The NMR spectra of the two toxins were identical and the IR spectra were superimposable. The two toxins also showed the same thin-layer chromatographic behavior in a variety of solvent systems, and it became apparent that tarichatoxin, from the eggs of the California salamander, was indeed identical to tetrodotoxin, isolated from the ovaries of the Japanese puffer fish.

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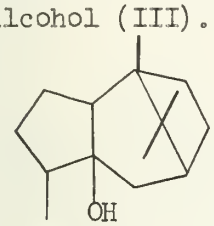
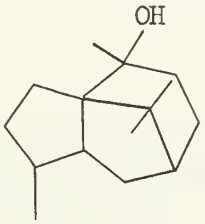
PATCHOULI ALCOHOL

Reported by Ronald J. Trancik May 10, 1965

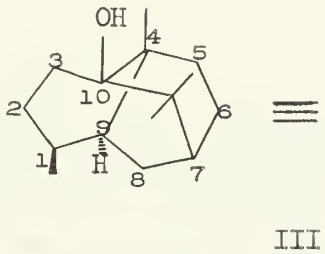
Introduction. - Patchouli oil is one of the most important and valuable raw materials used in the composition of perfumes.[1] The scent of the essence is partly due to patchouli alcohol, $C_{15}H_{26}O$, a tricyclic sesquiterpene first isolated by Gal[2] in 1869 from the leaves of Pogostemon patchouli var. suavis. Early structural investigations and a degradative structure determination by Treibs,[3] who in 1949 proposed (I) as a structural expression for this natural product, have been reviewed[4-7] and will not be discussed in this abstract. Since then structures (II)[6-9] in 1956 by Büchi and coworkers and (III)[10,11] in 1963 by Dunitz, Büchi and coworkers have been proposed. Structure (III) was the result of an x-ray analysis. It is the purpose of this seminar to review the structural developments and total synthesis of patchouli alcohol (III).



I

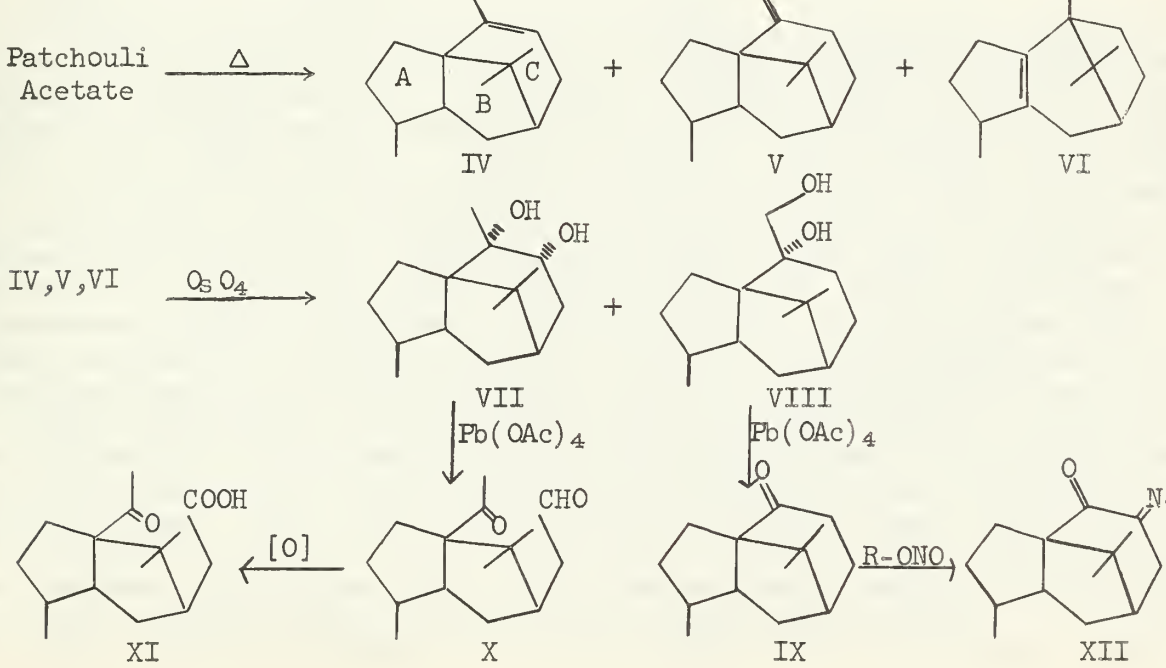


II

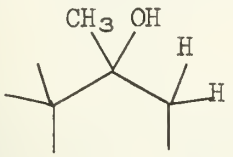


III

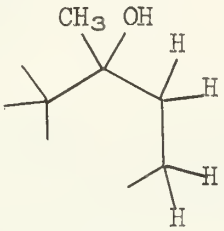
Structure Proof[8,12] - Patchouli acetate, prepared by the action of ketene on the natural product, was pyrolyzed affording a mixture of olefins and acetic acid. The distribution of isomers was found to be: α - patchoulene (IV), 52%; γ - patchoulene (V), 46%; and β - patchoulene (VI), 4%. This mixture was oxidized with osmium tetroxide from which α - patchouli diol (VII) and γ - patchouli diol (VIII) were separated. Diol (VIII) on cleavage with lead tetraacetate gave formaldehyde and norpatchoulione (IX) whose infrared spectrum exhibited a carbonyl at 1706 $cm.^{-1}$, excluding the presence of a substituted cyclopentanone.[13] Diol (VII) was oxidized with lead tetraacetate to ketoaldehyde (X) and further, upon exposure to air, to ketocarboxylic acid (XI). This evidence, along with the observations that norpatchoulione (IX) upon condensation with isoamyl nitrite afforded an α - oximino ketone (XII) instead of an oximino ester[14] and its low reactivity with 2,4-dinitrophenylhydrazine, suggested a carbonyl group next to a fully substituted carbon atom. The partial structure (XIIIa) was proposed for patchouli alcohol assuming that the acetate pyrolysis proceeded without rearrangement.



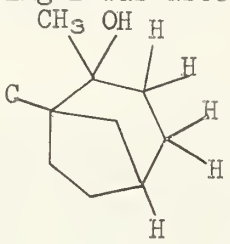
Evidence for the size of ring C was secured by oxidation of a mixture of α - and γ - patchoulene (IV and V) to give a dicarboxylic acid (XIV), $C_{13}H_{20}O_4$, which was dehydrated to an anhydride (XV). Formation of the dicarboxylic acid (XIV) was rationalized by partial structure (XIIIb) originally being present. The infrared spectrum of the anhydride (XV) possessed bands at 1786 $cm.^{-1}$ and 1754 $cm.^{-1}$ attributable to a glutaric anhydride,[15] and identical with those present in the spectrum of camphoric anhydride. This behavior was paralleled by the fact that camphoric acid but not homocamphoric acid forms an anhydride in the same manner.[3] This evidence led to a six membered assignment of ring C. The size of ring B was ascertained by



XIIIa

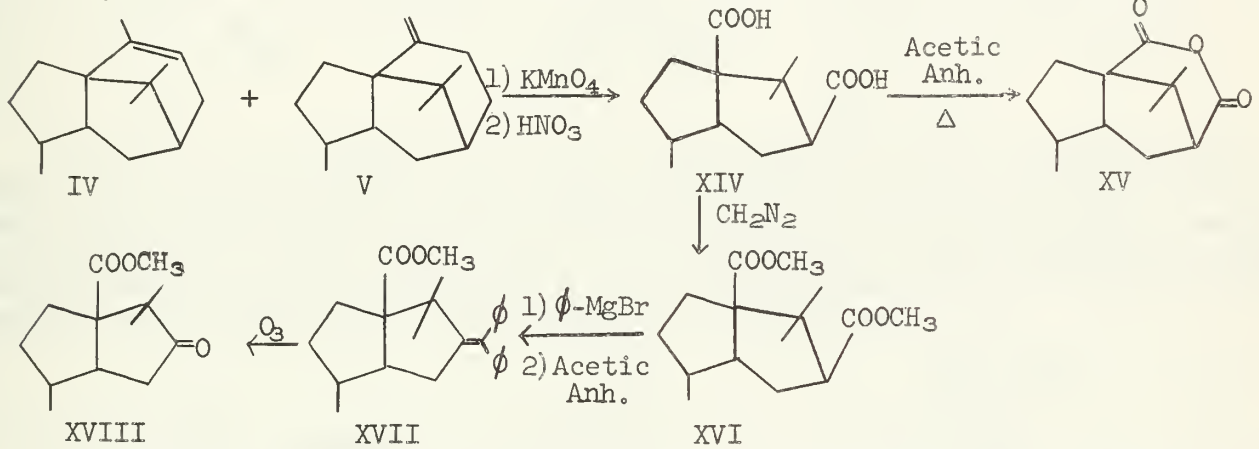


XIIIb



XIIIc

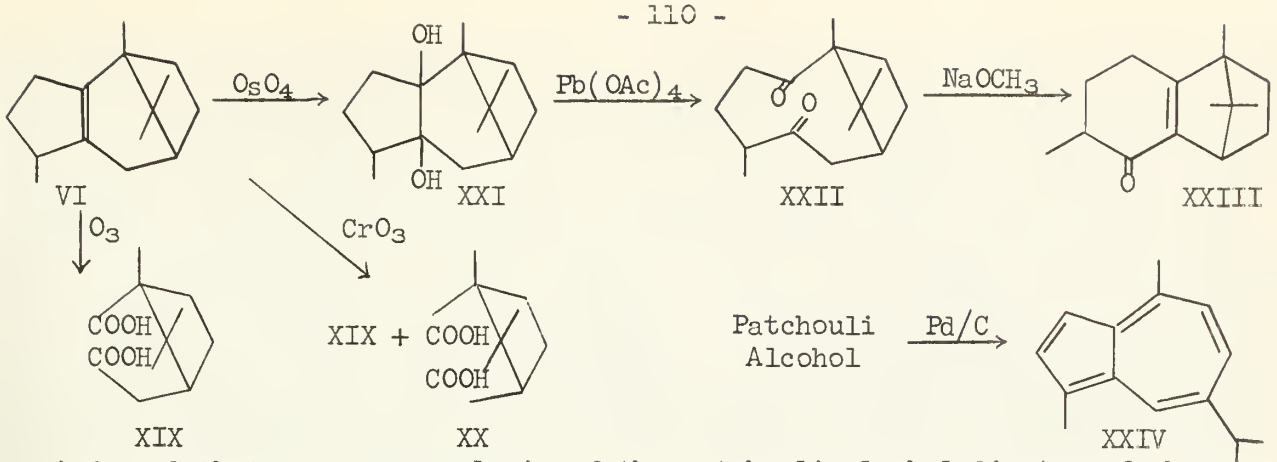
further degradations of norpatchoulidicarboxylic acid (XIV). Its dimethyl ester (XVI) was treated with phenylmagnesium bromide, dehydrated and oxidized with ozone to yield the ketoester (XVIII). The infrared spectrum of ketoester (XVIII) exhibited a carbonyl band at 1739 $cm.^{-1}$ which led to the assignment of ring B as being five membered.[13] Also, since one of the carboxyl groups in the diester (XVI) did not react with Grignard reagent, it was rationalized as being tertiary. Considering this evidence, partial structure (XIIIc) was now proposed as a possible representation.



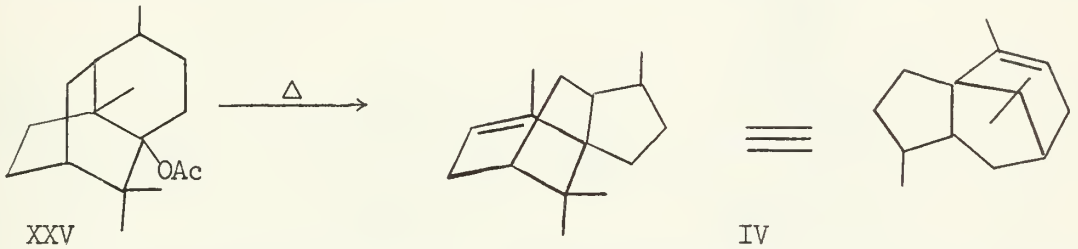
To further elucidate the structure of patchouli alcohol, β - patchoulene (VI), obtained by the dehydration or the acetate pyrolysis of patchouli alcohol, was next considered. Degradation of β - patchoulene (VI) with ozone yielded (+) - homocamphoric acid (XIX) while oxidation with chromium trioxide afforded (+) - homocamphoric acid (XIX) and (+) - camphoric acid (XX). The position of the double bond in β - patchoulene (VI) was established by reaction of this olefin with osmium tetroxide to yield a diol (XXI) which was oxidized with lead tetraacetate to a diketone (XXII) exhibiting a single carbonyl band in the infrared spectrum at 1695 $cm.^{-1}$. This diketone (XXII), which cyclized under various conditions to a cyclohexenone (XXIII), suggested a δ-diketone (XXII). β - patchoulene (VI) consequently was deduced to be a cyclopentene, and since the dehydrogenation of patchouli alcohol gave guaiazulene (XXIV), structure (VI) was proposed for β - patchoulene.

After consideration of the evidence outlined above, Büchi and coworkers proposed expression (II) as the structure of patchouli alcohol. β - patchoulene (VI) consequently arose via a Wagner - Meerwein rearrangement upon dehydration of patchouli alcohol (II). It was therefore not surprising that a mixture of α - and γ - patchoulene (IV and V) was converted quantitatively to β - patchoulene (VI) upon treatment with various acids. These rearrangements were apparently facilitated by release of steric strain present in the original ring system.

After publishing a synthesis of this alcohol (II) in preliminary form,[16] Büchi



was informed that an x-ray analysis of the patchouli alcohol diester of chromic acid, $C_{30}H_{50}O_4Cr$, revealed structure (III) for patchouli alcohol.[10] The diester was reconverted to the original alcohol by base hydrolysis or by lithium aluminum hydride reduction, thus excluding the possibility of a rearrangement in the course of esterification. Since the structure of α - patchoulene (IV) rests secure, the pyrolysis of patchouli acetate (XXV) must have been accompanied by an unprecedented rearrangement. Patchouli acetate (XXV) cannot lose the elements of acetic acid without rearrangement because the resulting olefin would violate Bredt's rule.[17]



Earlier,[12] in an effort to exclude a rearrangement in the acetate pyrolysis, Büchi and coworkers reconverted α - patchoulene (IV) to patchouli alcohol (II) by a route which was considered to be structurally unambiguous. This scheme is outlined in Fig. I. It was then realized that if structure (III) proposed by x-ray analysis was correct, one of the four steps in the α - patchoulene (IV) to patchouli alcohol sequence must have proceeded with skeletal rearrangement.

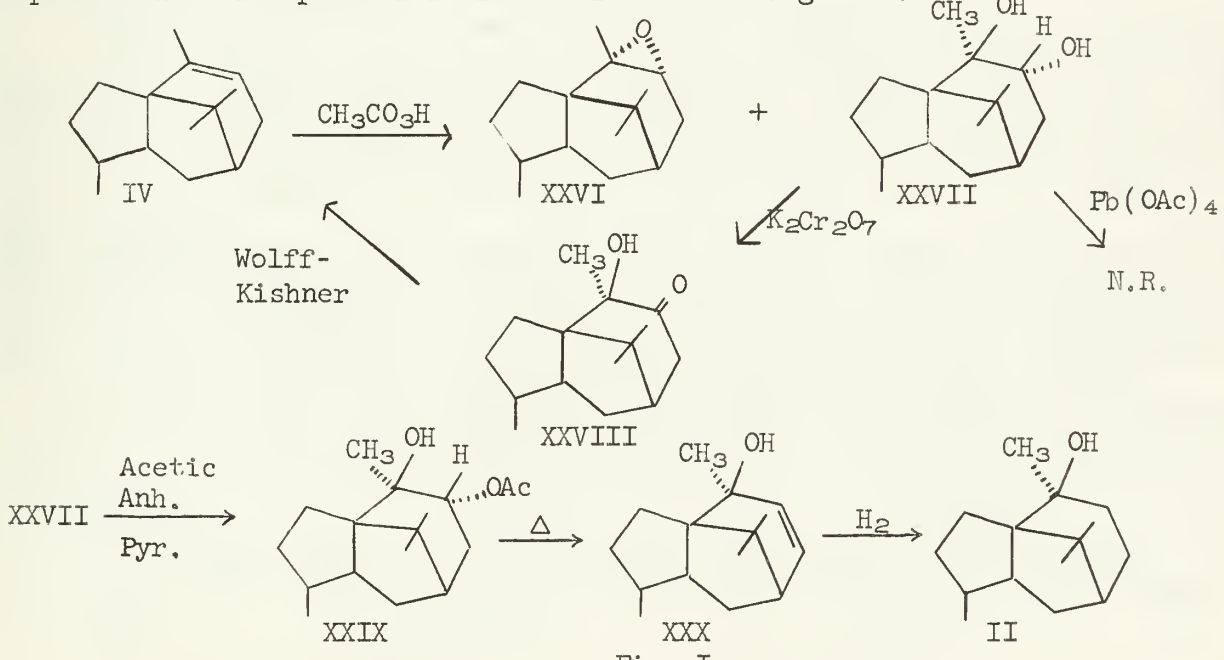


Fig. I

A reinterpretation of the evidence,[18] outlined in Fig. II, strongly suggested that a structural reassignment of acyloin (XXVIII) and diol (XXVII) was necessary.

Exposure of this hydroxyketone (XXVIII) to lithium aluminum hydride afforded a new diol which again was not cleaved by lead tetraacetate. Based on the earlier hypothesis, this new diol should have been the cis-1,2-diol which would have been readily oxidized by lead tetraacetate.[19] Therefore it was proposed that peracid oxidation of α - patchoulene (IV) did not yield the anticipated trans-diol (XXVII), and a rearrangement proceeding in precisely the reverse direction of that observed on pyrolysis of patchouli acetate was taking place. This was rationalized by rearrangement of a hypothetical β - epoxide (XXXI) to yield a rearranged 1,3-glycol (XXXII) by a stereoelectronically favored process. The mentioned hydroxyketone (XXVIII) was now proposed to have the structure (XXXIII). Both the monoacetate and the unsaturated alcohol derived from the 1,3-glycol (XXXII) were reformulated and represented by structures (XXXIV) and (XXXV). It was also pointed out that an additional Wagner - Meerwein rearrangement was operating in the dehydrogenation of patchouli alcohol (III) to guaiazulene (XXIV).

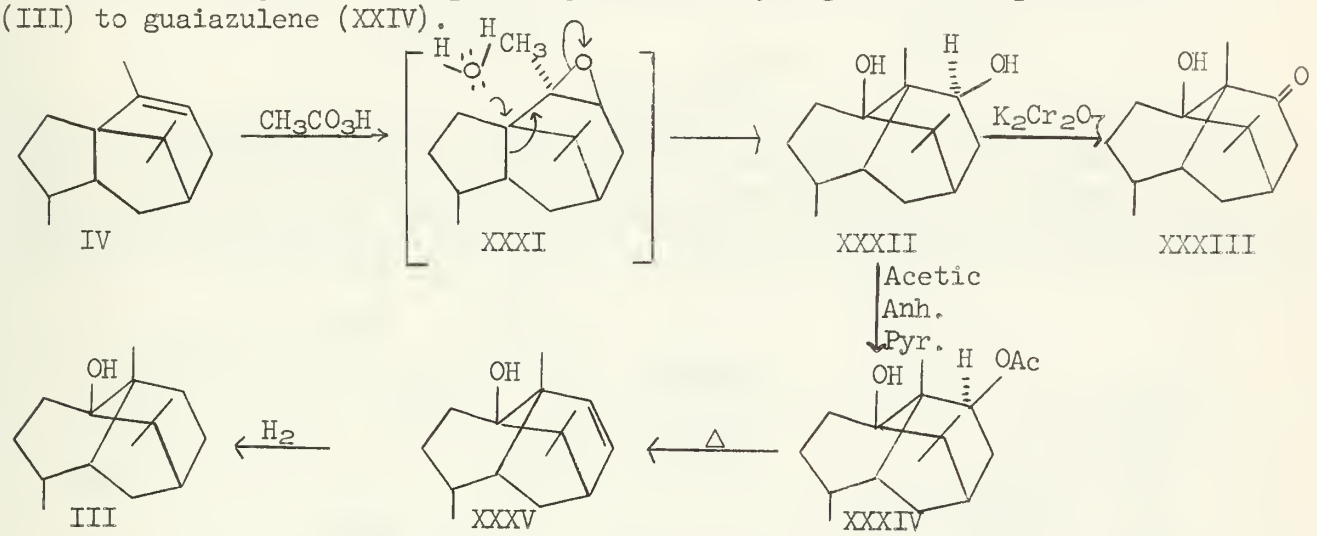


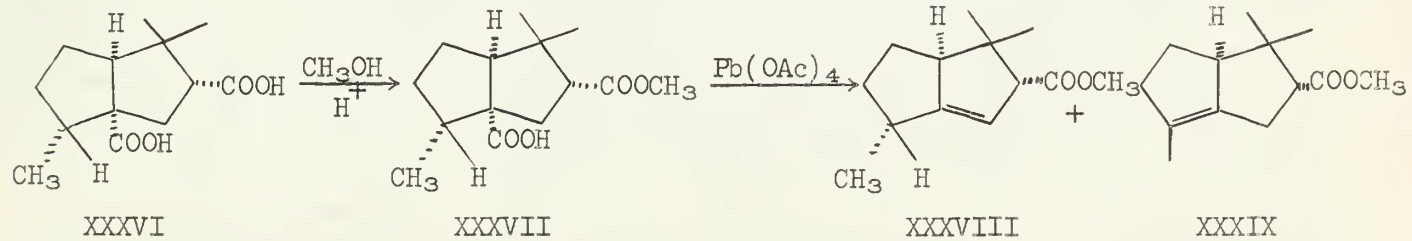
Fig. II

The configurations of the five asymmetric centers of patchouli alcohol (III) were now established. The configuration at C_7 was previously established[3,20] by conversion of β - patchoulene (VI) to (+) - camphoric and (+) - homocamphoric acids, both related to (+) - camphor of known absolute configuration. This correlation also determined the arrangement of substituents at C_{10}, C_9 and C_4.

The configuration at C_1 was established by comparison of norcedrenedicarboxylic acid (XXXVI), derived from cedrene of known stereochemistry,[21] with norpatchoulidicarboxylic acid (XL) obtained by the oxidation of a mixture of α - and γ - patchoulene (IV and V). Correlation of these two dicarboxylic acids was possible by removal of the tertiary carboxyl groups with lead tetraacetate. The scheme is outlined in Fig. III. The complete structure of patchouli alcohol was now represented by expression (III).

Total Synthesis.[16,18] - The approach to the synthetic sequence was one in which β - patchoulene (VI) figured as an important intermediate. The construction of this olefin appeared easier than a synthesis of α - patchoulene (IV). The success of such a scheme then depended on the ultimate transformation of β - patchoulene (VI) to a substance with the tricyclic framework of patchouli alcohol (III).

The first phase of the synthesis dealt with the attachment of a cyclopentane ring to (-) - homocamphor (XLIV) whose skeleton is contained in β - patchoulene (VI).



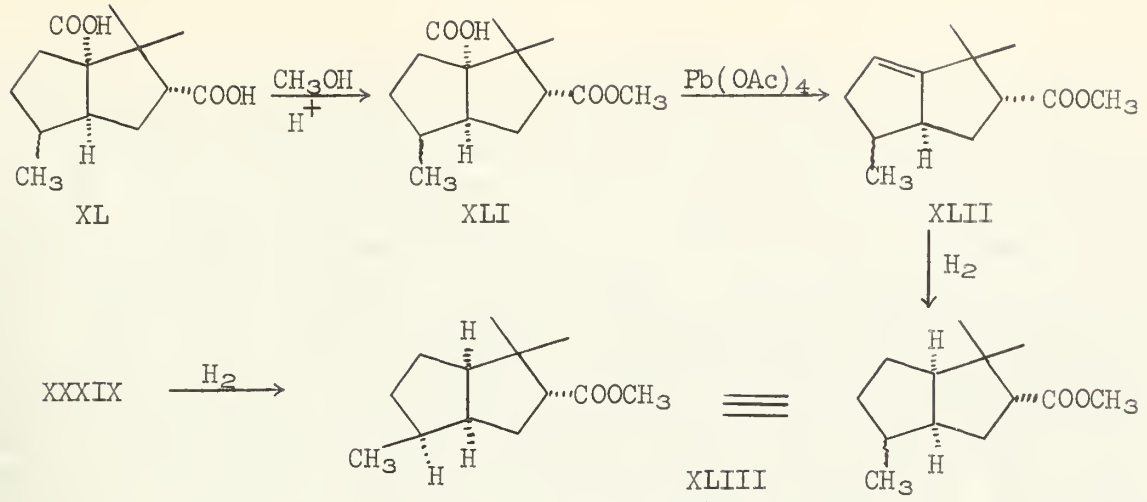


Fig. III

This was accomplished by the scheme outlined in Fig. IV. The addition of allylmagnesium chloride furnished the desired alcohol (XLV) with the conformation indicated, which was later verified by further transformations. Treatment of the unsaturated alcohol (XLV) with diborane followed by oxidation with Jones reagent yielded the spirolactone (XLVI) which rearranged to a mixture of two ketones (XLVII

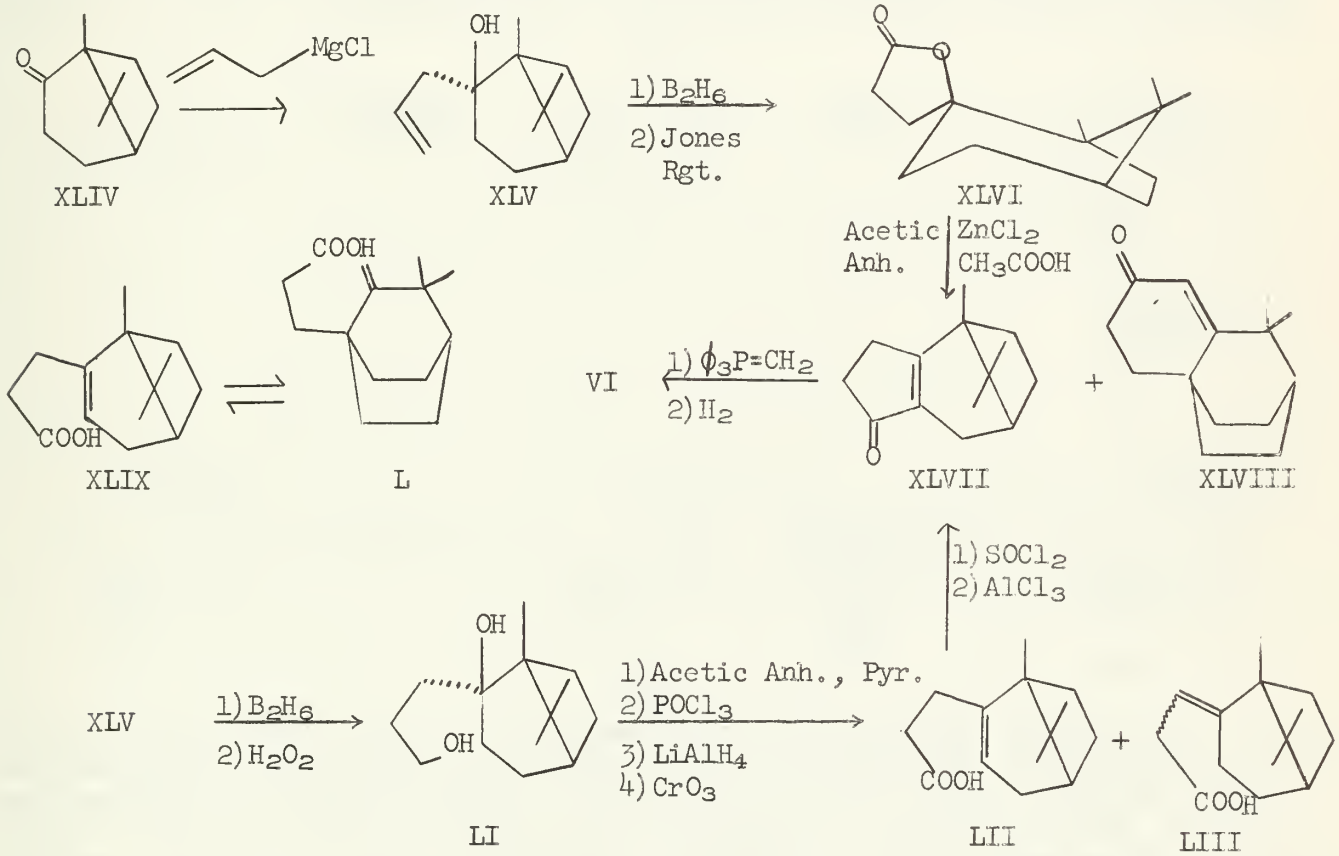


Fig. IV

and XLVIII) upon treatment with zinc chloride in a mixture of acetic acid and acetic anhydride. The major product was the desired cyclopentenone (XLVII) which was condensed with triphenylphosphinemethylene and immediately hydrogenated since the intermediate diene formed was highly labile. The optical rotation of the β-patchoulene (VI) ($[\alpha]_D=-4^\circ$) obtained by this synthetic route diverged markedly from that of a sample ($[\alpha]_D=-43^\circ$) originating from patchouli alcohol (III). This indicated that the cyclopentenone (XLVII) was largely racemic. This was rationalized by the two unsaturated acids (XLIX and L), proposed as precursors to the mixture of ketones (XLVII and XLVIII), participating in an equilibrium prior to dehydration to the corresponding tricyclic ketones (XLVII and XLVIII). This necessitated the

preparation of the unsaturated carboxylic acid (XLIX) by another route and of effecting its cyclization by a fast reaction in an aprotic solvent.

Treatment of the unsaturated alcohol (XLV) with diborane followed by oxidation, furnished the diol (LI) which was transformed directly into the unsaturated acid (LII) by successive treatments with acetic anhydride, phosphorous oxychloride in pyridine, lithium aluminum hydride and chromium trioxide. An NMR spectrum of the pure acid (LII) had signals at - 2.2 (1H), 4.9 (1H, broad), 9.0 (3H) and 9.08τ (6H). A spectrum of the crude acid revealed minor quantities of an isomeric unsaturated acid (LIII). The relative amounts of the two isomers produced suggested axial arrangement of the tertiary hydroxyl group[22] in the unsaturated alcohol (XLV) and thereby supported its conformation. The acid (LII) on treatment with thionyl chloride then aluminum chloride furnished the ketone (XLVII) whose spectral properties were identical with those of its racemic modification. $\underline{\beta}$ - patchoulene (VI) ($[\alpha]_D$=-42°) was then prepared by processes already discussed. This key intermediate contains a third asymmetric carbon atom and the resulting configuration (exo) was rationalized by assuming catalyst approach from the more accessible $\underline{\alpha}$ side.

The second phase of the synthesis was concerned with the rearrangement of $\underline{\beta}$ - patchoulene (VI) to $\underline{\alpha}$ - patchoulene (IV). This was accomplished by the sequence outlined in Fig. V. Oxidation of $\underline{\beta}$ - patchoulene (VI) with peracetic acid yielded

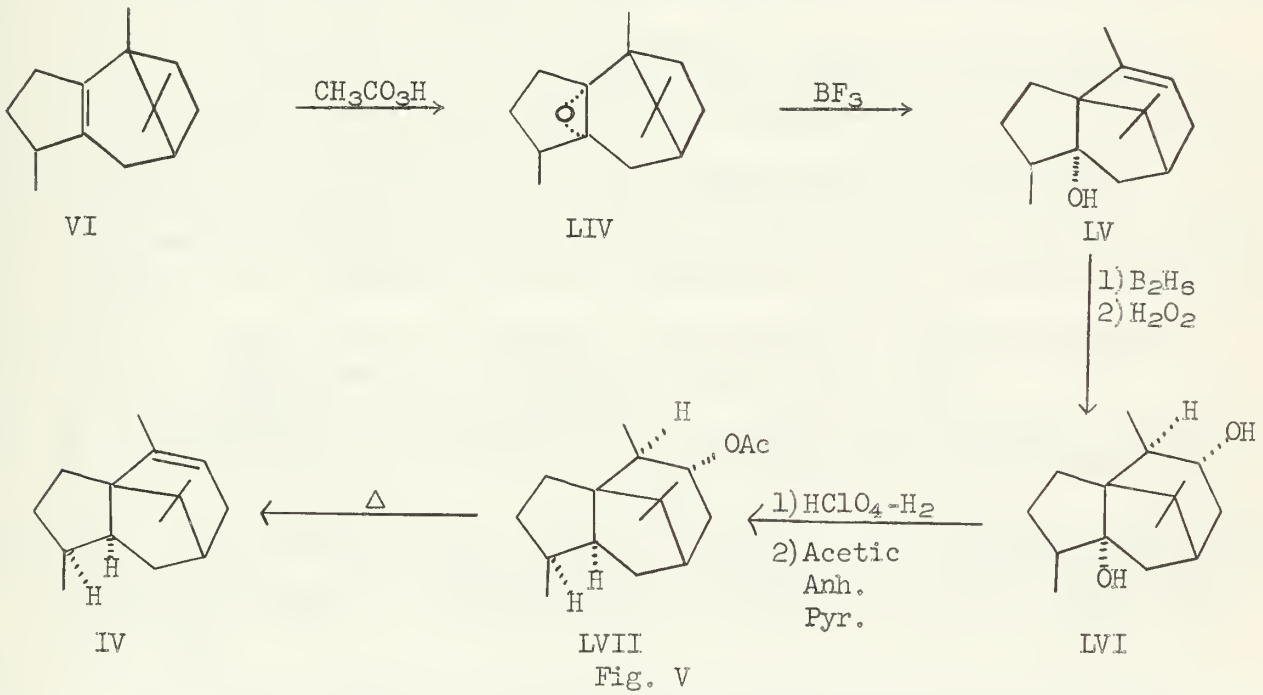


Fig. V

the $\underline{\alpha}$ - epoxide (LIV) which, on treatment with boron fluoride, underwent the desired rearrangement to the unsaturated alcohol (LV). The structure of the alcohol (LV) was verified by its NMR spectrum: 4.57 (1H, broad), 7.73 (1H), 8.35 (3H, singlet), 9.0 (3H, doublet), 9.05 and 9.14 τ (6H). Treatment of this alcohol (LV) with diborane - hydrogen peroxide yielded the diol (LVI). It then remained to eliminate the hydroxyl groups without simultaneous return to the $\underline{\beta}$ - patchoulene (VI) skeleton. This was achieved by catalytic reduction in the presence of perchloric acid and pyrolysis of the subsequent acetate (LVII) to yield $\underline{\alpha}$ - patchoulene (IV).

The final phase of the synthesis dealt with the conversion of $\underline{\alpha}$ - patchoulene (IV) to patchouli alcohol (III). This previously discussed transformation is outlined in Fig. II and constitutes a total synthesis of patchouli alcohol (III).

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FRIEDEL-CRAFTS ISOMERIZATIONS OF ALKYL- AND HALOBENZENES

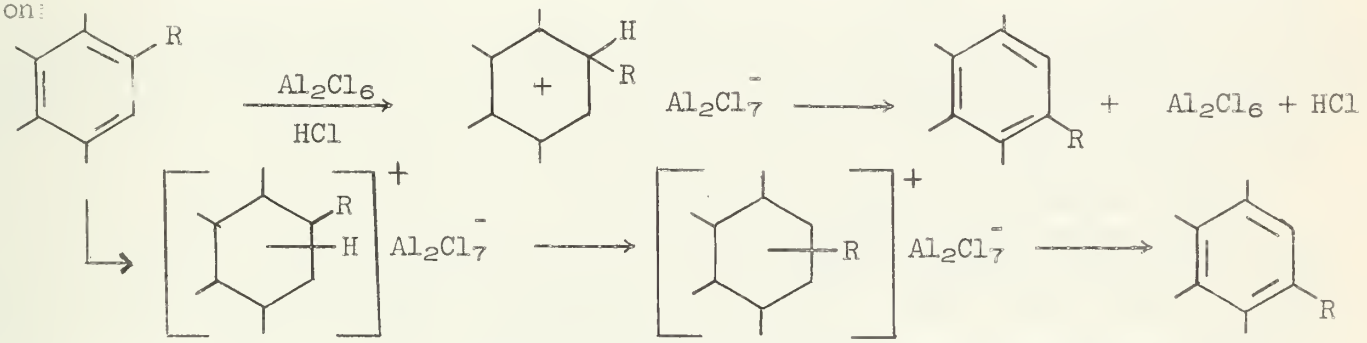
Reported by Bill Foglesong May 13, 1965

INTRODUCTION. - The reactions which alkylbenzenes undergo when treated with Friedel-Crafts catalysts can be classified into the following main types: isomerization, disproportionation, rearrangement, dealkylation, and fragmentation. In addition to isomerization and disproportionation as in alkylbenzenes, halobenzenes undergo two further reactions, halogen exchange and coupling. This seminar will be restricted primarily to a discussion of the isomerization reaction; the other types will be discussed only where their inclusion contributes to the understanding of the main topic.

Early work pertaining to the isomerization reaction has been reviewed by Thomas,[1] Price,[2,3] and Nightengale.[4] Reviews of more recent work have been published by McCauley[5] and Roberts.[6]

ISOMERIZATION OF ALKYLBENZENES. - Although electronic theory predicts 1,2 and 1,4 substitution in alkylation reactions, early studies[1,2,3,4] indicated the formation of large amounts of products with 1,3-orientation. These results were explained both by dealkylation of 1,2,4 isomers[2-a] and by isomerization of 1,2 or 1,4 isomers.[2-b] The issue was confused by the great variety of reaction conditions employed and by the lack of accurate analytical techniques. Nightengale summed up early work with the following statement: "Again it must be emphasized that there are much conflicting data in the literature and that no one theory seems adequate to explain these data".[4] This section will describe recent work which has cleared up some of this early confusion.

Contrary to a report by earlier workers[7] that the rate of isomerization of xylenes with aluminum chloride was unaffected by the presence of hydrogen chloride, Braddeley and co-workers[8,9] found that the reaction did not proceed without a catalyst such as hydrogen chloride. For example, p-xylene remained unchanged after contact with excess aluminum bromide at room temperature for one day. However, when one mole of hydrogen bromide was added under otherwise similar conditions, 67% m-xylene was obtained. Less than 1% disproportionation products were observed. On the basis of these studies Braddeley proposed the following mechanisms for alkylbenzene isomerization:



These mechanisms are in accord with the hydrogen exchange observed when deuterium chloride is passed into a mixture of benzene and aluminum chloride.[10]

In 1950 McCaulay and co-workers[11,12] began an extensive study of the action of hydrogen fluoride - boron trifluoride on methylbenzenes. The relative basicities of the methylbenzenes in boron trifluoride - hydrogen fluoride were determined. The results are summarized below. It is evident that the basicity of a particular hydrocarbon depends both on the number and on the orientation of its methyl groups. It was also found that these aromatic hydrocarbons form complexes containing one mole of boron trifluoride per mole of hydrocarbon. Identical molar lowering of the vapor pressure of hydrogen fluoride by the complex and by potassium fluoride indicated that the complex consisted of two ions, probably ArH^+ and BF_4^-.[11] The cation was postulated to be a sigma complex (Figure I).

RELATIVE BASICITIES OF SOME METHYLBENZENES

toluene	0.01
p-xylene	1
o-xylene	3
m-xylene	9
pseudocumene	18
durene	60
mesitylene	1400

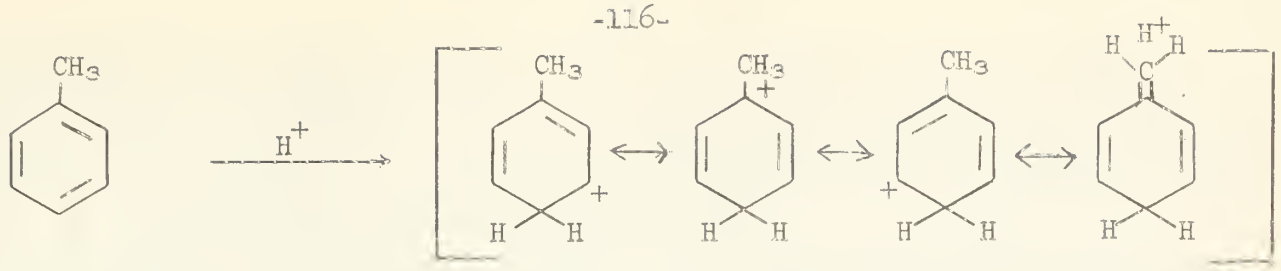
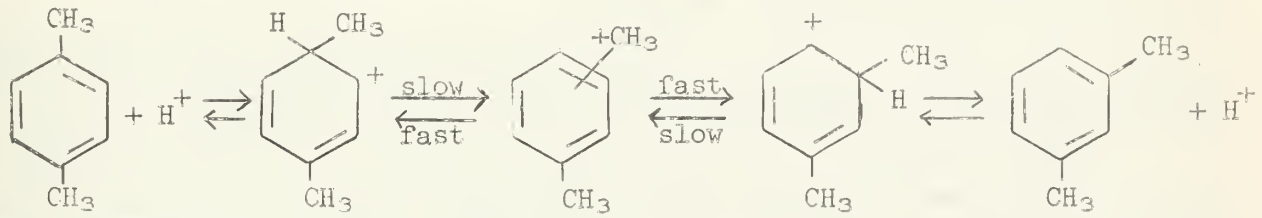


Figure I

Sigma complexes were also proposed by Brown and co-workers to account for the interaction between alkylbenzenes, aluminum chloride, and hydrogen chloride.[13]

McCaulay and Lien[14] also studied the isomerization of methylbenzenes with boron trifluoride-hydrogen fluoride Using low BF_3/hydrocarbon ratios and temperatures from 82°-121°, they found that the product compositions agreed closely with the equilibrium compositions determined by Taylor.[15] For example, starting with any xylene isomer, an equilibrium mixture consisting of 19% o-, 60% m-, and 21% p-xylene was obtained, whereas Taylor's gas phase determination of the thermodynamic equilibrium ratios gave 18% o-, 58% m-, and 24% p-xylene. Little disproportionation or direct ortho - para interchange was observed. When higher concentrations of boron trifluoride were employed the concentration of the meta isomer at equilibrium was much higher. This was attributed to selective complexing of the meta isomer by the excess catalyst.[14] These results suggested to McCauley and Lien a mechanism resembling that proposed previously by Braddeley.[8,9] However the initial complexes and transition states were given more attention in keeping with the observed experimental facts. Their mechanism is illustrated below with p-xylene.



Brown and Jungk's study[16] of xylene isomerization with aluminum bromide-hydrogen bromide confirmed the mechanistic conclusions previously reached by Braddeley[8,9] and McCauley.[14] However, second order kinetics for the isomerization was observed rather than first order kinetics as reported by McCaulay. The reaction was nevertheless still felt to be a unimolecular rearrangement of a sigma complex, with the second order kinetics arising from an equilibrium distribution of protons between the toluene solvent used and the o- and p-xylene undergoing isomerization. The actual 1,2-alkyl shift was postulated as occurring either through a transition state where the alkyl group is shared by adjacent ring carbons (Figure II-a) or by an intermediate high energy localized π-complex (Figure II-b).

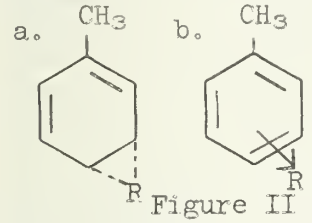


Figure II

The absence of direct ortho-para interconversion of the xylenes rules out the possibility of an unlocalized π-complex in which the methyl group is relatively free to move about the π-electron cloud of the benzene nucleus.[16]

A kinetic study by Allen and Yats[17] of the equilibration of xylenes in toluene solution confirmed the 1,2-shift mechanism proposed above. The following relative rate constants were found:

$K_{po} = 0$	$K_{om} = 3.6$	$K_{mp} = 2.1$
$K_{op} = 0$	$K_{mo} = 1.0$	$K_{pm} = 6.0$

Still further evidence for 1,2-shifts has been obtained by Steinberg and Sixma[18] from a study of the isomerization of toluene-1-^{14}C under the influence of aluminum bromide-hydrogen bromide.

In 1964 Suld and Stuart[19] studied the isomerization of dimethylnaphthalenes with anhydrous hydrogen fluoride and boron trifluoride. As in the case of methylbenzenes it wa

concluded that isomerization proceeds by way of an intramolecular 1,2-methyl shift. However, contrary to the previous case where methyl groups were free to migrate completely around the benzene nucleus, it was found that with naphthalene there exist a number of discrete groups of equilibrating isomers with facile isomerization possible within a group but with no interconversion of isomers belonging to the different groups. The following equilibrium groups were found:

2,6-DMN ⇌ 1,6-DMN ⇌ 1,5-DMN ; 2,7-DMN ⇌ 1,7-DMN ⇌ 1,8-DMN

2,3-DMN ⇌ 1,3-DMN ⇌ 1,4-DMN ; 1,2-DMN ⇌ no other DMN isomers

From the isomer composition of the groups it is evident that there exist migrational barriers between the adjacent β-β' positions as well as between the two rings of the naphthalene nucleus. Similar results were obtained by Russian workers[20] from a study of the isomerization of 1-methyl-1-^{14}C-naphthalene over a heterogeneous catalyst. These migrational barriers were rationalized by Suld and Stuart on the basis of differences in stabilities of the activated complexes leading to isomerization. For example, the failure to observe β-β' shifts was explained by the small resonance contribution of the high energy quinoid complex shown in Figure III-a compared with that of the more favorable form shown in Figure III-b.

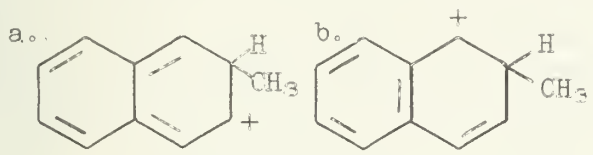


Figure III

The rates of isomerization of the various naphthalene isomers were the same order of magnitude as those observed in the isomerization of xylenes[14] with the exception of the 1,4 and 1,8 isomers which isomerized much more rapidly than any of the others. No explanation was given for the higher isomerization rates of these two isomers.

When the side chains are longer than methyl, the situation becomes more complex. Both the rate of isomerization and the rate of disproportionation increase as alkyl groups replace the aliphatic protons in methylbenzenes. These rates seem to increase with increasing ability of the migrating alkyl group to bear positive charge.

However, while their rates of isomerization and disproportionation are considerably greater than methylbenzenes, ethylbenzenes still isomerize primarily by an intramolecular 1,2-shift mechanism.[21,22] In a study of the isomerization of ethyltoluenes with aluminum chloride in toluene at 25° Allen[21] obtained the following relative rate constants:

$k_{po} = 1.0$ $k_{mo} = 5.3$ $k_{pm} = 60.8$

$k_{op} = 2.9$ $k_{om} = 38.3$ $k_{mp} = 24.6$

The low values of k_{po} and k_{op} indicate that the isomerization proceeds primarily by 1,2-ethyl shifts. Olah[22] arrived at a similar conclusion in the case of the isomerization of diethylbenzenes with water-promoted aluminum chloride. As evidence for the predominance of isomerization by the 1,2-shift mechanism he cited that in the isomerization of o-diethylbenzene, an initial buildup of m-diethylbenzene is observed before the formation of an appreciable amount of p-diethylbenzene and that the rate of isomerization decreases in the presence of added benzene.[22] However, work by Unserer and Wolf[23] on the disproportionation of ethylbenzene-1-^{14}C under the influence of aluminum bromide and hydrogen bromide is not in accord with isomerization solely by a 1,2-shift. After treating ethylbenzene-1-^{14}C with aluminum bromide-hydrogen bromide for 17 minutes at 0° the carbon-14 label in the recovered ethylbenzene was distributed as is shown in Table 1. If the isomerization had proceeded predominantly by way of 1,2-ethyl shifts, one would have expected the largest portion of label to be in the ortho positions rather than in the para position as was observed. Although the work of Allen[21] and Olah[22] appears to be more reliable, a final judgement must await further experimental work.

ETHYLBENZENE-1-^{14}C ISOMERIZATION

position	label
1	58%
2,6	9%
3,5	15%
4	18%

Table 1

Allen and co-workers[24] obtained the

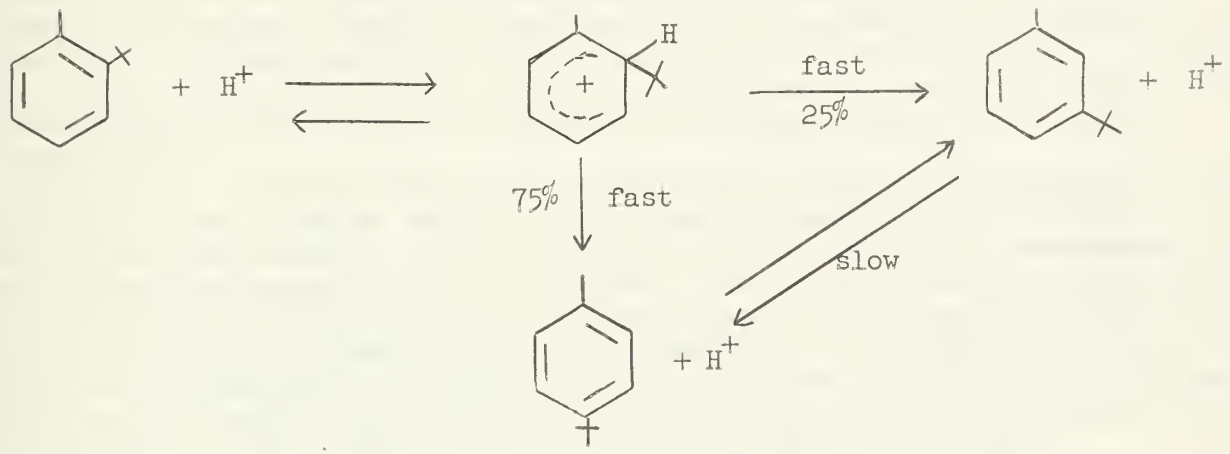
following relative rate constants for the isomerization of cymenes (isopropyltoluenes) in toluene with aluminum chloride - hydrogen chloride:

$k_{om} = 45.8$ $k_{mp} = 2.4$ $k_{po} = 1.0$

$k_{mo} = 1.0$ $k_{pm} = 5.5$ $k_{op} = 19.8$

From these rate constants it was concluded that the isomerization of cymenes in toluene did not proceed primarily by a 1,2-shift. Rather it was proposed that the mechanism involves an intramolecular delocalized π-complex or an intermolecular alkylation-dealkylation or both. The difference in mechanisms of the xylenes and cymenes was explained by the hypothesis that in σ-complexes the isopropyl group dissociates as a carbonium ion more readily than does a methyl group in the same position.[24] In the isomerization of diisopropylbenzenes, Olah[25] postulated a 1,2-shift of an isopropyl group as the primary mode of reaction. Evidence cited for the 1,2-shift was the initial buildup of m-diisopropylbenzene when o-diisopropylbenzene was isomerized. However, Olah's data cannot rule out isomerization occurring partially by the mechanisms proposed above by Allen.

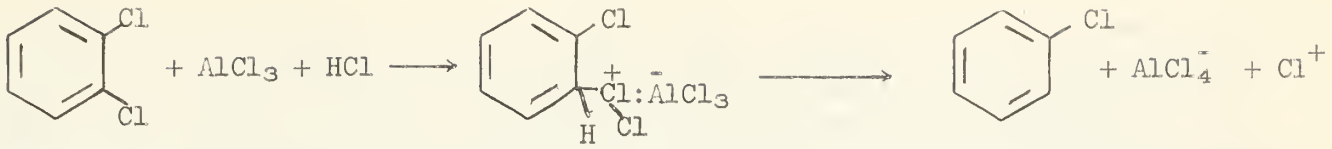
The isomerizations of di-t-butylbenzenes and t-butyltoluenes clearly seem to be of a different nature than the isomerization of ethyl- and methylbenzenes. For example, whereas in the isomerization of o-xylene[14] or o-diethylbenzene[22] a large initial buildup of the meta isomer is observed before formation of appreciable amounts of the para isomer, in the case of o-di-t-butylbenzene[24] or o-t-butyltoulene[25] an initial buildup of para isomer is observed followed by a slower conversion to the equilibrium mixture. The results may be illustrated by the following scheme:



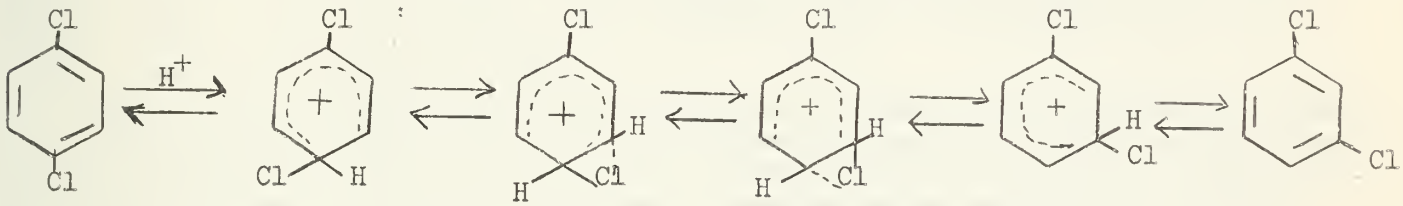
This fast initial ortho-para conversion may be explained either by complete detachment of the t-butyl group followed by electrophilic attack on another molecule or by intramolecular isomerization via a delocalized π-type intermediate.[26,27] Olah feels that the π-complex-type transition state is in best accord with the observed high rate of isomerization of o-di-t-butylbenzene under high dilution conditions. However, the large amount of disproportionation observed tends to support at least partial isomerization by an intermolecular process.

ISOMERIZATION OF HALOBENZENES. - Halogen migration in aromatic compounds under Friedel-Crafts conditions has been frequently investigated. A review of early work appeared by Thomas in 1941.[1] This section will discuss more recent developments.

In 1958 Spryskov and Erykalov[28,29] began a study of the isomerization of dichlorobenzenes under the influence of aluminum chloride. At 160°, after 50 hours, o-, m-, and p-dichlorobenzene each isomerized to give the same equilibrium mixture of 16% o-, 30% p-, and 54% m-dichlorobenzene. The formation of disproportionation products occurred to only a small extent (<2%). It was proposed that the aluminum chloride produces dehalogenation of dichlorobenzene with the formation of monochlorobenzene and liberation of chlorine. The latter chlorinates monochlorobenzene, forming a mixture of dichlorobenzenes. Dehalogenation was postulated to proceed through a donor-acceptor mechanism as illustrated below:



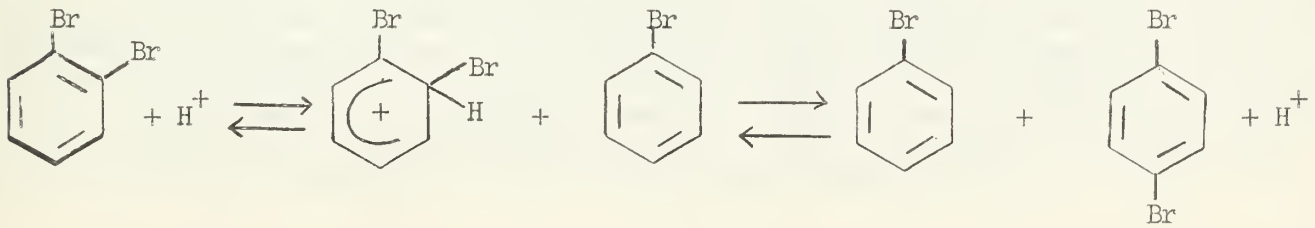
The intermediacy of a free positive chlorine species, as indicated in the above scheme, is difficult to accept. By analogy with electrophilic substitution it would be expected to attack chlorobenzene preferentially in the ortho and para positions. One might therefore expect an initial buildup of p-dichlorobenzene in the isomerization of o-dichlorobenzene. Such is the case in the disproportionation of bromobenzene with aluminum bromide.[30] The dibromobenzene formed initially consists of about 85% p- and 15% o-dibromobenzene as would be expected for the bromonium ion postulated. However, an initial buildup of the para isomer is not observed when o-dichlorobenzene is isomerized. Instead the concentration of the meta isomer is found to pass through a maximum early in the reaction.[28,31] This observation plus the lack of disproportionation products led Olah to propose the mechanism illustrated below:



A 1,2-shift mechanism of this type explains the experimental facts better than Spryskov and Erykalov's dehalogenation-rehalogenation mechanism. It should be pointed out that while Spryskov and Erykalov did not postulate isomerization by 1,2-chlorine shifts, their data supports such a mechanism. A mechanism similar to Olah's has also been suggested for the isomerization of chloronaphthalenes by Vorozhtsov[32] and by Weingarten.[33]

In the case of difluorobenzenes[31] no isomerization or disproportionation was observed even under vigorous reaction conditions (14 days, 240°). The only products isolated other than starting material were chlorofluoro- and dichlorobenzenes, which arose from halogen exchange with the catalyst. The inability of difluorobenzenes to undergo Friedel-Crafts isomerizations was attributed to the inability of fluorine to form the positively polarized entity which presumably is necessary to achieve intramolecular or intermolecular isomerization. An alternate explanation is that the electronegative fluorine atom imparts a partial positive charge to the adjacent carbon atom and thereby makes protonation at that carbon unfavorable.

As opposed to difluorobenzenes (no isomerization) and dichlorobenzenes (isomerization at elevated temperatures), dibromobenzenes isomerize readily at room temperature when treated with water-promoted aluminum bromide.[34-a] Initial buildup of the meta isomer is not observed in the isomerization of o- or p-dibromobenzene as it was in the analogous dichlorobenzenes. Instead, a fast ortho-para interchange leading to a quasi-stationary ortho-para ratio of about 1:6.5 followed by a slower conversion to the thermodynamic equilibrium mixture (62% meta, 4.5% ortho, and 33.5% para) is observed. This initial ortho-para ratio is the same as that obtained in the electrophilic bromination of bromobenzene.[34] This suggested to Olah that the isomerization of bromobenzenes proceeds intermolecularly by way of a positively charged bromine species (in limiting case of the bromonium ion, Br^+) as indicated below:

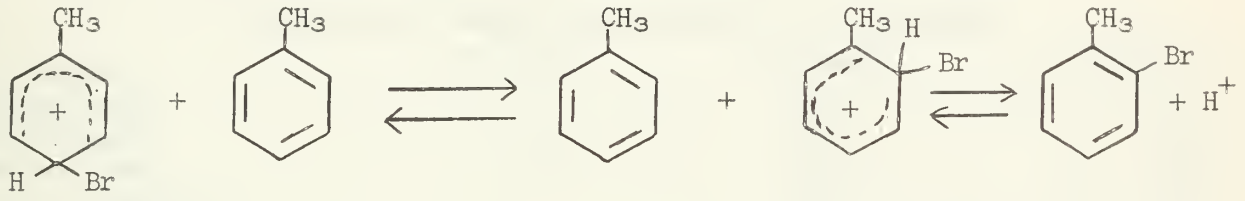


The fact that dibromobenzene disproportionates almost quantitatively to bromobenzene in the presence of excess benzene was cited by Olah as additional evidence for the intermolecular nature of the rapid ortho-para interconversion. A similar conclusion was reached by Kooyman and Louw[34-b] from a study of dibromobenzene isomerization in the presence of excess chlorobenzene and other acceptors. The slower conversion to the meta isomer was postulated to proceed by means of a 1,2-shift as discussed earlier for chlorobenzene isomerization.

The isomerizations of chloro- and bromofluorobenzenes[31,34] proceed analogously to those of dichlorobenzenes and dibromobenzenes, respectively. However, the rates of isomerization of o-chlorofluorobenzene and o-bromofluorobenzene are unusually slow compared to the rates of isomerization of o-dichlorobenzene and o-dibromobenzene. Olah attributes this low reactivity to the electronic deactivating effect of the adjacent fluorine atom.[31,34]

Olah and co-workers[35] have also studied the aluminum chloride catalyzed isomerization of fluoro-, chloro- and bromotoluenes. At 100° p-chloro- and p-fluorotoluene show an initial buildup of meta isomer before formation of appreciable amounts of ortho isomer, as is characteristic of a 1,2-shift. Since chlorobenzene and fluorobenzene were the predominant disproportionation products, it was concluded that the methyl group is the migrating entity.

Bromotoluenes isomerize much more rapidly than fluoro- and chlorotoluenes, reaching equilibrium in 15 minutes at 100°. In contrast to the isomerization of p-fluoro- and p-chlorotoluenes, Olah found that with p-bromotoluene there was an initial buildup of o-bromotoluene followed by a slower conversion to the equilibrium mixture. Olah explained these results by postulating detachment of a bromine atom from the protonated p-bromotoluene complex with subsequent or simultaneous attack of the bromonium ion on a toluene molecule:



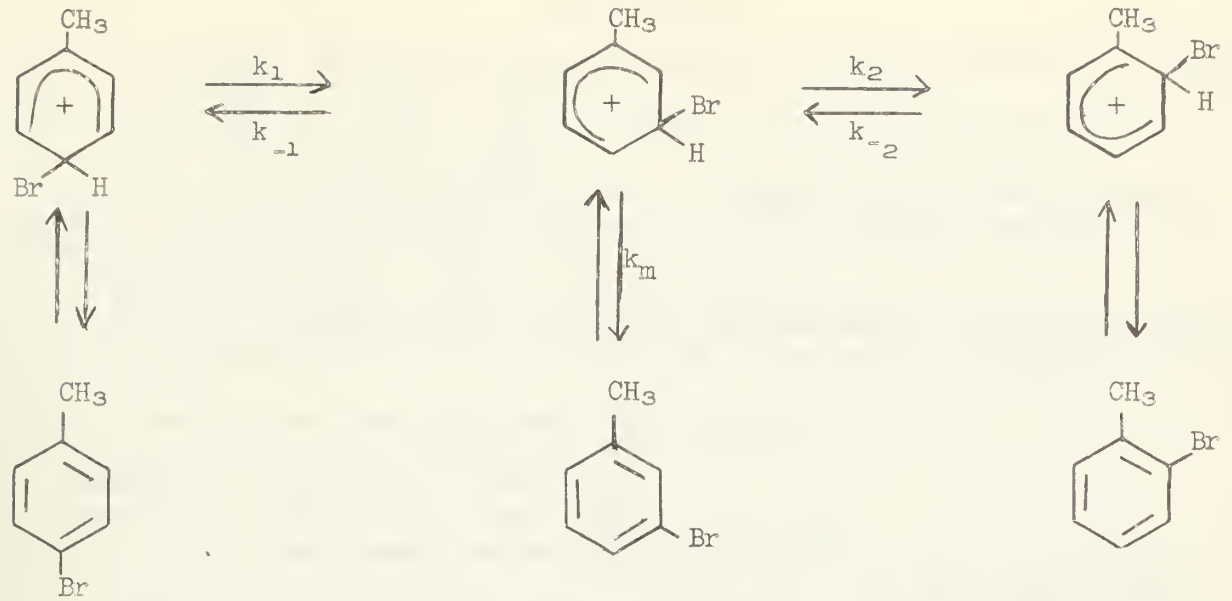
The formation of m-bromotoluene could occur either by a slower 1,2-shift in o-bromotoluene and p-bromotoluene, or its buildup could result from the fact that intermolecular bromination-debromination occurs preferentially at the ortho and para positions (where it is reversible), but debromination does not occur to any substantial degree at the meta position (where protonation is not favored). When methyl was replaced by ethyl in the above three halides the results were qualitatively the same.[31]

Crump and Gornowicz[37] also studied the isomerization of bromotoluenes. Treating their data in a manner similar to that used by Allen and co-workers,[24] they obtained the following relative rate constants when bromotoluenes were isomerized with anhydrous aluminum bromide in excess toluene:

$k_{mp} = 1.5$ $\quad k_{op} = 6.0$ $\quad k_{po} = 13.4$

$k_{mo} = 1.0$ $\quad k_{om} = 1.2$ $\quad k_{pm} = 4.2$

Since the k_{op}/k_{om} and k_{po}/k_{pm} ratios indicate the positional selectivity to be low, it was concluded that m-bromotoluene formation (and isomerization) occurs principally by an intramolecular 1,2-shift, even in the presence of excess toluene. In the isomerization of p-bromotoluene in the absence of solvent, no increase in the rate of o-bromotoluene formation was observed during the reaction even though a slow steady buildup in the toluene concentration occurred. This is not consistent with isomerization solely by an intermolecular mechanism. They felt that the following mechanism was more consistent with their experimental observations,



where k_{-1}, k_2, and k_m are of comparable magnitude.[37] Intramolecular isomerization of bromotoluenes by this method is similar to the isomerization of t-butyltoluenes and di-t-butylbenzenes by the unlocalized π-complex mechanism discussed earlier. Operation of such a mechanism should also be considered for the isomerizations of dibromobenzenes, bromochlorobenzenes, and bromofluorobenzenes.

A chart containing the equilibrium isomer compositions of some of the substituted halobenzenes which have been studied is shown below.

EQUILIBRIUM ISOMER DISTRIBUTION OF HALOBENZENES

compound	% ortho	% meta	% para
difluorobenzene	-	-	-
dichlorobenzene	8	60	32
dibromobenzene	4.5	62	33.5
fluorochlorobenzene	4	64	32
fluorobromobenzene	5	63	32
chlorobromobenzene	5	62	33
fluorotoluene	31	56	13
chlorotoluene	31	44	25
bromotoluene	38	44	18
fluoroethylbenzene	36	52	12
chloroethylbenzene	28	52	20
bromoethylbenzene	24	56	20

It is interesting to note that all dihalobenzenes show a low percentage of the ortho isomer compared to the haloalkylbenzenes. The low percentage of ortho isomer in the dihalobenzenes could be due to the fact that two electronegative atoms adjacent to each other is energetically unfavorable.

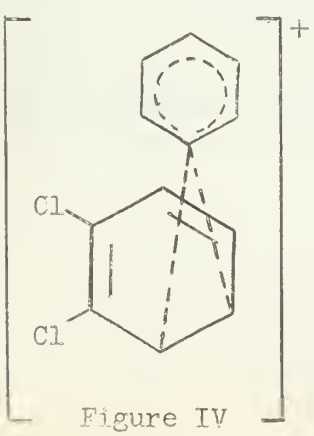


Figure IV

In 1962 Weingarten[38] reported that the isomerization of chlorinated biphenyls with an aluminum chloride-hydrogen cloride catalyst proceeds predominantly by phenyl migration via a 1,2-intramolecular shift. A phenonium ion (Figure IV) was postulated as an intermediate or transition state in this reaction.

In a study of the isomerization of fluorinated biphenyls Olah[39] proposed a similar intermediate.

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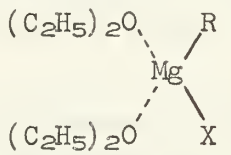
THE STRUCTURE OF ORGANOMAGNESIUM HALIDES

Reported by Adriane Gurak May 17, 1965

Since the discovery of the Grignard reaction in 1900,[1] the structure of the reagent involved has offered a challenging and frustrating problem to numerous workers. This seminar will discuss mainly the work done in this field since 1961 with reference being made to earlier studies only as they are related to the more recent ones. Several reviews of work to 1961 are available.[2,3,4,5]

Early formulations of the structure of the Grignard reagent were varied and presented controversy. However, a number of these formulations, although less refined, do not differ considerably from those being considered at present. Grignard postulated the structure I, initially just to represent the stoichiometry of the reaction he had discovered[1] and later as a possible structure.[6] He also considered the dimeric form II.[7] In 1912, Jolibois postulated the structure III on the basis of observed enhanced solubility of diethylmagnesium in an ether solution of magnesium iodide.[8] Meisenheimer and Casper[9] postulated the structure IV in opposition to the oxonium salts being considered as probable structures at the time.

$RMgX$ (I) $\quad (RMgX)_2$ (II) $\quad R_2Mg \cdot MgX_2$ (III)



IV

As early as 1905, the existence of equilibrium (1) had been considered.[10] In 1929, Schlenk and Schlenk[11] substantiated this suggestion with their dioxane precipitation experiment, whereby solvated magnesium dihalide was precipitated and dialkylmagnesium left in solution upon addition of dioxane to an ether solution of the Grignard reagent. These workers accepted the existence of equilibrium (1) and

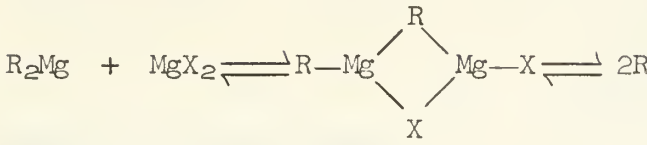
$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \quad (1) \qquad R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2 \quad (2)$$

discounted the existence of equilibrium (2) since, they felt, the latter equilibrium would necessitate a concentration dependence which was not observed. The validity of the above described precipitation experiment as a means of studying the Grignard species has since been questioned on the basis of the sensitivity of the equilibrium to experimental conditions.[12] Also, explanations to validate the existence of a dimeric species, despite the fact that Schlenk and Schlenk did not observe concentration dependence in their precipitation experiment, have been offered.[3,13,14] At any rate, the precipitation method was generally abandoned as a meaningful method for determining the nature of the Grignard species. The work instead took the form of comparison of equimolar solutions of dialkylmagnesium and magnesium dihalide with the Grignard reagent, molecular weight studies, spectral investigations, X-ray work, and a few other methods.

Comparison of equimolar R_2Mg and MgX_2 solutions with the Grignard reagent: The Schlenk equilibrium denotes the possibility that an equimolar solution of a dialkylmagnesium and a magnesium dihalide might be equivalent to the Grignard reagent. Chemical evidence has attempted to demonstrate this equivalence.[15,16] Although these works indicate such equivalence (i.e., the rates of reaction with 1-hexyne or benzophenone of such equimolar solutions and the corresponding Grignards are essentially equal), it must also be considered that the possibility of the reactive species of an equimolar solution of dialkylmagnesium and magnesium dihalide being identical to that of the Grignard reagent does not necessitate that the structure of the Grignard reagent is identical with the structure of the species in the equimolar solution.

Dessy found that the dielectric constants of an equimolar solution of diethylmagnesium and magnesium bromide and the corresponding Grignard were equivalent.[17] The dubious value of this evidence has been discussed elsewhere in light of the bulk nature of the dielectric constant measurement.[5] Still further, it has recently been pointed out[18] that the break in a plot of dielectric constant versus $(C_2H_5)_2Mg/MgBr_2$ ratio at a one to one ratio of the two components, which had been observed by Dessy, cannot distinguish between a monomeric or dimeric species. For example, a monomeric

species might be postulated to form as shown in (3). This monomeric species, I, could then dimerize to form II; or it might remain as the monomeric species. It might also be imagined that R_2Mg and MgX_2 combine to form III. Also, aside from the fact that one cannot really ascertain what the species is that is formed upon combination of R_2Mg and MgX_2, it could well be that this species is not representative of the Grignard reagent.



$$R_2Mg + MgX_2 \rightleftharpoons R\text{—}Mg\text{—}Mg\text{—}X \rightleftharpoons 2RMgX \quad (3)$$

As has been considered elsewhere,[5,18,19] conductance studies[20] have also led to dubious results with respect to the equivalence of the solutions discussed above. A recent note[21] has indicated that ethylmagnesium chloride in tetrahydrofuran is equivalent to the corresponding equimolar solution of diethylmagnesium and magnesium chloride with respect to conductance and dipole moment, but this one result does not lend itself to a general discussion.

Assuming equivalence of equimolar solutions of dialkyl or diarylmagnesium and magnesium dihalide and the corresponding Grignard reagent solutions, Dessy and co-workers have studied ether solutions of magnesium labeled $MgBr_2$ and unlabeled R_2Mg where R is ethyl[22] or phenyl.[23] In neither experiment did $Mg^{28}Br_2$ exchange considerably with R_2Mg (e.g., after 36 hours, the statistical exchange in the $(C_2H_5)_2Mg$ case was 8 per cent). This was interpreted in light of the structure III as opposed to II. The fact that when $Mg^{25}Br_2$ was used, complete exchange occurred was essentially overlooked and ascribed to an impurity. This work has been criticized,[5,18] but for the most part workers have accepted the above results as quite conclusive evidence for structure III. A recent note by Dessy and co-workers,[24] however, points out that the nature of the above magnesium exchange study is not at present interpretable. Their experiments indicate that whether statistical exchange occurs or not is perhaps dependent on the variables of magnesium source, method of preparing R_2Mg and MgX_2, solvent and/or separation reagent.

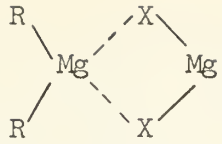
It might also be noted that Roberts and co-workers[57] reported, in a recent communication, statistical exchange between "high purity" $Mg^{25}Br_2$ and unlabeled ethylmagnesium bromide.

Molecular weight studies: Slough and Ubbelohde[25] found that the degree of association of Grignard reagents varied from monomeric (e.g., p-methoxyphenylmagnesium bromide) to trimeric (e.g., cyclohexylmagnesium bromide) at a concentration of approximately 0.3M (in [RMgX] units) depending upon the Grignard reagent employed. They also noted that with increasing concentration and with excess magnesium bromide the Grignard reagent association increased while it decreased with increasing temperature. In addition, these workers found that the degree of association increased when the Grignard reagent was contaminated with only a trace of oxygen; and hence they discredited some of the earlier molecular weight studies.[26,27]

Employing a concentration range of 0.1 to 0.3M, Ashby and Becker[21] determined by means of ebullioscopic measurements that ethylmagnesium bromide and ethylmagnesium chloride are monomeric in tetrahydrofuran. Employing a "wide concentration range", they found that ethylmagnesium chloride (as well as mesitylmagnesium bromide) were dimeric in diethyl ether. One essentially common result to both solvent systems was the isolation of $(C_2H_5)Mg_2Cl_3$ from the tetrahydrofuran system upon addition of benzene and the isolation of $(CH_3)Mg_2Cl_3$ from a diethyl ether solution of methylmagnesium chloride (assumed to be dimeric, although this was not specifically stated by the authors). They rationalized the results in the tetrahydrofuran system to imply the existence of equilibrium (4) and extended the equilibrium in the dimeric case (perhaps to the exclusion of the monomeric species) to include species V and/or VI, with preference for V indicated on the basis of steric reasoning. Although this work provides a feasible basis for rationalizing structure V, it by no means negates structure VI; and the fact that RMg_2X_3 could not be isolated from a diethyl ether Grignard solution, at least in the

$$3RMgX \rightleftharpoons 3/2R_2Mg + 3/2MgX_2 \rightleftharpoons RMg_2X_3 + R_2Mg \quad (4)$$

V



VI

case of ethylmagnesium chloride, could indicate for diethyl ether solutions that the solubility of RMg_2X_3 is dependent on the R group or perhaps specific combinations of the R and X groups. It could also indicate the non-existence of alkyl exchange (i.e., of the equilibrium involving RMg_2X_3) in certain cases.

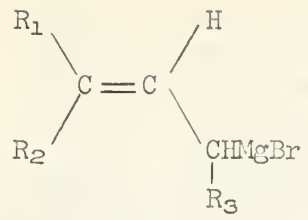
Vreugdenhil and Blomberg, using extremely careful experimental conditions to exclude the presence of any trace impurities, found ethylmagnesium bromide to be monomeric in both ether[28] and tetrahydrofuran[29] when a concentration range of about 10^{-2} to 10^{-3} M was employed. They also noted that excess magnesium bromide (to the extent of about 3 per cent of the Grignard reagent content) did not increase the degree of association of the Grignard reagent. They concluded that the Schlenk equilibrium (1) exists while the equilibrium (2) does not. The limited concentration range they employed, however, leaves the general nature of their conclusion open to question. Also, the change in degree of association of the Grignard reagent with excess magnesium bromide might be a concentration dependent phenomena; and hence it might not have been observed in their experiments because of the low concentrations used.

A study of the degree of association of the Grignard reagent in diethyl ether as a function of concentration as well as halogen has recently been reported.[18] A sample of the results are indicated in Table I. From this data one might obviously conclude a monomeric Grignard reagent from alkyl bromides and iodides tending toward a dimeric species with increasing concentration. For the alkylmagnesium chlorides, although the results are not as straightforward as for the bromides and iodides, one might rationalize that the chloride reagent tends toward a monomeric species at concentrations more dilute than 10^{-2} M. However, it still might be argued that the measured increasing degree of association with increasing concentration is due to oxygen or some other impurity, since this work did not as rigorously exclude these as the Vreugdenhil and Blomberg work did.[30] Therefore, although increasing association with increasing concentration is probable, it is not conclusive.

Table I

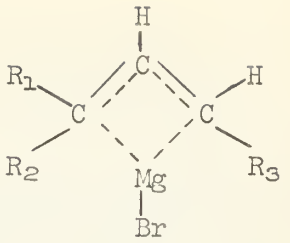
Grignard reagent	Concentration, moles [RMgX]/l.	i, molecular weight/formula weight
"C_2H_5MgCl"	0.086	1.87
	0.143	1.86
	0.196	1.92
"C_2H_5MgBr"	0.035	1.00
	0.102	1.04
	0.150	1.16
	0.200	1.26
	0.249	1.37
"C_2H_5MgI"	0.055	1.00
	0.108	1.12
	0.158	1.27
	0.204	1.36

Spectroscopic Studies: Nuclear magnetic resonance has been used by Roberts and co-workers to study a series of allylmagnesium halides VII-a,b,c,d[31-34] as well as compounds VIII and IX.[35] The spectra of VII-a,b,c,d studied allowed these workers to conclude an equilibrium such as (5) existed as opposed to structures X and XI. For example, in the case of allylmagnesium bromide (VII-a) an AX_4 spectrum was observed. If the structure were X, an AM_2X_2 spectrum might be expected, as has been observed for an allylpalladium compound.[36] The reasons for excluding XI are not as clear. Initially Roberts and co-workers excluded this anion structure on the basis of the room temperature spectrum of VII-a, since they felt that the cis and trans protons of XI should be different. Later, when they noted that the spectrum exhibited no change to -80°C, their view was substantiated but not really proven. At any rate, this abandonment of structure XI might be thought valid if one considers the lack of evidence for anions in Grignard solutions.[3] When VII-b,c,d were studied, the primary Grignard reagents were found, by means of chemical shift analyses, to be the predominant isomers (e.g., the spectra of VII-b and VII-c were identical and the



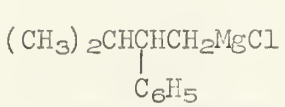
VII-a VII-b VII-c VII-d

R_1	H	CH_3	H	CH_3
R_2	H	H	H	CH_3
R_3	H	H	CH_3	H

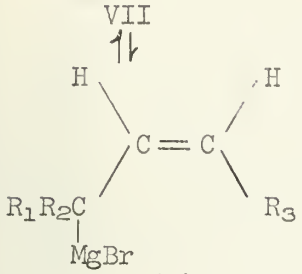


$(CH_3)_3CCH_2CH_2MgCl$

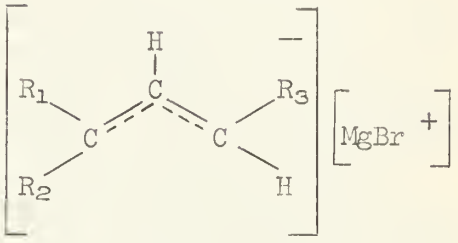
VIII



IX



(5)



XI

chemical shifts and spin-spin splittings corresponded to those one would predict for the spectrum of VII-b). In the case of VII-d, cooling of the sample from +33 to -55°C resulted in a broadening and then splitting into a doublet of the originally singlet proton resonance of methyl groups R_1 and R_2. The calculated ΔH is $7^{+}_{-}3$ kcal./mole for the cis and trans methyl group interchange. For compounds VIII and IX, Roberts and co-workers concluded a rapid rate of inversion at the carbon-magnesium bond. For example, the methylene protons of the $-CH_2Mg-$group of VIII exhibited an A_2X_2 spectrum at +33°C which became an AA'XX' spectrum at -50°C. Considering the separation of the outer intense lines of the AA'XX' spectrum as being equal to the sum of the vicinal coupling constants, the possibility of a difference in conformer populations causing these observed spectra was negated since this should have necessitated a change in the separation of the outer intense lines with temperature, an effect which was not observed. However, inversion at the carbon-magnesium bond was compatible with the temperature dependent spectra. Hence, NMR, at least in the cases of compounds VII, VIII and IX, is able to give evidence about the structure of the Grignard reagent; but it also leaves a number of questions unanswered. For example, whether the species is monomeric or dimeric cannot be concluded.

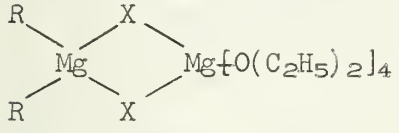
Fraenkel and co-workers have recently reported work analogous to the above studies on compounds VIII and IX.[37,38] Again, however, although this work may give evidence concerning the structural unit, it is quite inconclusive with respect to the entire structure.

Evans and Maher[39] have reported a NMR study of methyl-, ethyl- and propylmagnesium halides and their corresponding dialkylmagnesiums. Basing their study on an observation of Roberts and co-workers that the spectra of dibutenylmagnesiums do not differ considerably from those of the corresponding Grignards and hence cast doubt on formulation I as the Grignard structure,[32] they noted analogous results with their systems. They cited also that the spectrum of dimethylmagnesium was concentration dependent while that of methylmagnesium iodide was not concentration dependent to any considerable extent. Hence, they concluded that dimethylmagnesium was polymeric and dissociated on dilution while the Grignard structure was quite stable, not being affected by dilution. In accord with the results of Dessy and co-workers[15,17,20,22,23] and their NMR data, they felt that the Grignard structure must be III.

It is not clear why the above work of Evans and Maher necessitates structure III. If the similarity of the spectra of the dialkylmagnesium and the corresponding Grignard excludes structure I, then it would seem reasonable that III, as well as II, should be excluded, especially if they are envisioned as VI or V, respectively. At any rate, be the structure monomeric or dimeric, the presence of halogen in the species containing the alkyl group would be expected to affect the chemical shift pattern of the alkyl group NMR spectrum. However, although the above work of Evans and Maher indicates that NMR may be capable of showing that the dialkylmagnesium and Grignard solutions are distinct (by means of concentration dependence studies), it is not necessarily able to distinguish between these solutions by means of chemical

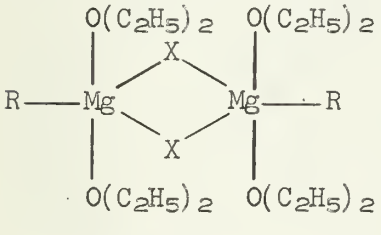
shifts. Still further, molecular weight studies previously discussed in this abstract have indicated that ethylmagnesium bromide[18,28] and methylmagnesium iodide[18] are predominantly, if not entirely, monomeric for the concentrations studied by Evans and Maher. lower range of the

Roos and Zeil[40] have examined the concentration dependence of the chemical shift values for diethylmagnesium, equimolar solutions of diethylmagnesium and magnesium dihalide, and the corresponding Grignards in diethyl ether and tetrahydrofuran solutions and have also examined the concentration dependence of the solvent chemical shifts for the above solutions and for an ether solution of magnesium iodide. They noted that for concentrated solutions (>1M) the chemical shift values for dialkylmagnesiums and the corresponding alkylmagnesium halides were different with this difference vanishing upon extrapolation to infinite dilution. This is in agreement with an observation made independently by Stucky and Rundle[41] for diphenylmagnesium and phenylmagnesium bromide etherates. Roos and Zeil also noted that equimolar solutions of dialkylmagnesium and magnesium dihalide exhibited NMR spectra and concentration dependencies essentially identical to those of the corresponding Grignards. A break in the graphs of concentration versus $[\sigma_{CH_3}-\sigma_{CH_2}]$ (where σ represents chemical shift) for the organometallic component of either diethyl ether or tetrahydrofuran solutions at a value corresponding to two moles ether per mole magnesium was interpreted by these authors to indicate coordination of two moles ether per [RMgX] unit. The observation that the solvent $[\sigma_{CH_3}-\sigma_{CH_2}]$ for diethyl ether solutions of either ethylmagnesium iodide or magnesium iodide were identical was interpreted to indicate that the ether was coordinated in an analogous manner in both species. Hence Roos and Zeil concluded that XII was a probable structure for the Grignard reagent with the unsolvated magnesium atom tetrahedrally coordinated and the other octahedrally coordinated, basing XII, in part, on a dimeric MgX_2 structure.



XII

The Roos and Zeil work, however, has several points which obscure its conclusions. For one thing, only one set of chemical shift values for the solvent was observed (i.e., the NMR spectra made no distinction between coordinated and solvent ether). One might rationalize, as the authors did, that solvent exchange is occurring at a rate rapid on a NMR time scale. Nevertheless, the experimental fact of a single chemical shift set leaves the interpretation inconclusive. Secondly, Roos and Zeil assumed a dimeric Grignard. The molecular weight studies of Ashby and co-workers seem to substantiate this assumption.[18,21] If, however, it is reasoned that these molecular weight studies are in error, perhaps due to the effects of contamination, then it is equally reasonable that the monomeric structure IV could be the Grignard species. Still further, XIII might also be reasonable, rather than the dimeric species XII, since nothing really definite can be said about the chemical shifts of the ether protons.



XIII

It might also be noted that Roos and Zeil found an equivalence between the NMR spectra of equimolar solutions and the corresponding Grignards. Evans and Maher had also found an indication of this in their work on methylmagnesium iodide.[39] However, as has been stated earlier, the attainment of this equivalence does not answer the basic question of what the Grignard structure is.

An infrared study on dialkyl and diarylmagnesiums, equimolar solutions of dialkyl- and diarylmagnesiums and magnesium dihalides, and the corresponding Grignard reagents has recently been made for diethyl ether and tetrahydrofuran solutions.[42] Using the aid of an experimentally established equation, these workers decided on a region for the carbon-magnesium bond of 500-535 $cm.^{-1}$ for alkyl groups and a region of 365-383 $cm.^{-1}$ for aryl groups. They studied the above spectra from this basis. The spectra of the Grignard reagents from methyl, ethyl and phenyl bromide or iodide (in diethyl ether) and methyl, ethyl and phenyl chloride or bromide (in tetrahydrofuran) were identical with those of the corresponding equimolar solutions of dialkyl- or diarylmagnesium and magnesium

dihalide. In tetrahydrofuran, the bands of the spectra of methylmagnesium chloride and bromide were distinct enough so that the equilibria obtained in these systems could be studied. No concentration dependence was observed in these cases and thus the existence of equilibrium (1) rather than (2) was concluded. The equilibrium constants were estimated from the spectra to be 4.5 and 3.5 for methylmagnesium chloride and bromide, respectively. The Grignards from ethyl chloride and bromide and phenyl bromide in tetrahydrofuran were stated to show the same spectral characteristics as the above methyl halide Grignards, but their bands were not distinct enough to allow estimation of equilibrium constants. Phenylmagnesium chloride in tetrahydrofuran and all Grignards, except phenylmagnesium iodide, studied in diethyl ether were said to show spectra from which no definite conclusions could be drawn. The spectrum of phenylmagnesium iodide in diethyl ether was interpreted to indicate the existence of equilibrium (1) rather than (2) because of its similarity to the interpretable spectra of the tetrahydrofuran solutions.

The above interpretation assumes a correct assignment of the dialkylmagnesium and alkylmagnesium halide bands (i.e., the observation of an increase in the intensity of the methylmagnesium halide carbon-magnesium band and a decrease in the intensity of the dimethylmagnesium carbon-magnesium band upon addition of excess magnesium bromide to the system assumes that one is actually observing the carbon-magnesium bands). The experiments of Ashby and Becker[21] indicate that the above Grignards are monomeric in tetrahydrofuran for the concentrations used in studying their IR spectra, an observation which lends support to the above spectral interpretation. One is still left, however, with the problem of accounting for the enhanced solubility of magnesium dihalide observed, at least in the cases of the methyl Grignards, in tetrahydrofuran when the existence of equilibrium (1) is assumed.

The identical spectra for equimolar solutions and the corresponding Grignards in both diethyl ether and tetrahydrofuran is good evidence that the two systems are the same. Again, however, it leaves the nature of the Grignard reagent undecided.

No rigorous UV studies of the Grignard reagent have been reported. However, UV has been used in an attempt to establish the organic part of cinnamylmagnesium bromide.[43]

X-ray studies: Stucky and Rundle have reported the single crystal X-ray determination of phenylmagnesium bromide dietherate[41,44] as well as an oxidation product of the same Grignard.[30] They also have noted that a three dimensional structure determination of ethylmagnesium bromide dietherate has been completed.[44,58] Both the phenyl- and ethylmagnesium bromide dietherates were determined to be monomeric with the magnesium tetrahedrally coordinated.

This data is quite conclusive, but unfortunately it can only definitely be applied to a solid state description of the Grignard reagent and can say little of the anomalous effects that may occur upon dissolving the Grignard reagent in ether. Also, the solid was obtained by concentration of the Grignard solution. Hence, one might assume some series of equilibria with this solid representing only the least soluble species of these equilibria and not necessarily the predominant species.

Stucky and Rundle[41] have rationalized that the Grignard solution is probably monomeric following basically the reasoning that: one, species such as $(C_6H_5)_2 \cdot Mg \cdot MgBr_2 \cdot n(C_4H_{10}O)$ are unlikely since n would probably be two or less, a condition for which Stucky and Rundle observed polymerization; and two, species such as XIII would have the correct ether to magnesium ratio but would be thermodynamically unfavored. Thermodynamic unfavorability in the latter case is based on the greater strength of the Mg-O bond as compared to the Mg-Br bond and on entropy considerations.

The structure XII proposed by Roos and Zeil[40] might be considered an alternate possibility to those structures negated by Stucky and Rundle (i.e., $(C_6H_5)_2 \cdot Mg \cdot MgBr_2 \cdot 2(C_4H_{10}O)$ and/or XIII). Stucky and Rundle,[44] however, reasoned that since magnesium bromide is probably monomeric (according to the studies of Slough and Ubbelohde[25] and Vreugdenhil and Blomberg[28]), the NMR comparison by Roos and Zeil of magnesium dihalide and alkylmagnesium halide solvation should be applied to monomeric species. Nevertheless, it should be pointed out that the molecular weight determinations of magnesium bromide cited by Stucky and Rundle were done at relatively low concentrations (approximately 10^{-2}M) and hence suffer from lack of a study of the dependence on concentration of the degree of association of magnesium bromide.

Other studies: By means of a gas chromatographic method of measuring partial pressures, ether (solvent)-tetrahydrofuran (cosolvent) solutions of Grignards were examined to determine the degree of complexing of co-solvent per [RMgX] unit.[45] From this procedure, it was concluded that one tetrahydrofuran unit is bound per the Grignard units [C_2H_5MgBr], [C_6H_5MgBr] and [$C_6H_5CH_2MgBr$].

This work has been interpreted to indicate bonding of one solvent molecule per [RMgX] unit[19,46] and hence to cast doubt on formulations such as IV for the Grignard species in solution. However, replacement of one diethyl ether molecule by one tetrahydrofuran molecule per [RMgX] unit does not necessitate that only one diethyl ether molecule was bound per [RMgX] unit, as the authors themselves pointed out[47] in a comment related to the X-ray work of Stucky and Rundle. It might also be pointed out that measurement of one tetrahydrofuran molecule complexed per [RMgX] unit does not really indicate the species to which tetrahydrofuran is complexed.

Walborsky and Young[48-50] have studied the optically active Grignard reagent prepared from (+)-(S)-1-bromo-1-methyl-2,2-diphenylcyclopropane. Their work indicates a significant amount of non-ionic character to the carbon-magnesium bond of the Grignard reagent. Also, Wright and co-workers[51] have found that an optically active ether (e.g., (+)-2,3-dimethoxybutane) will induce optical activity in the product alcohol from the reaction of a Grignard reagent (e.g., methylmagnesium chloride) with an optically inactive substrate (e.g., benzaldehyde). This latter work indicates a coordinate bond of the solvent ether to the Grignard reagent in solution. However, neither work is especially definitive with respect to the Grignard structure.

Besides the kinetic studies cited previously in this abstract for the comparison of equimolar solutions and the corresponding Grignard solutions, kinetic investigations of the Grignard reaction have been made in an attempt to gain evidence about the structure of the Grignard reagent. These investigations and their relation to the Grignard structure have been discussed elsewhere.[18,19,46] It might also be noted that some recent kinetic work[55,56] has indicated a monomeric Grignard species for low concentrations by means of first order kinetics observed for a ketone (2,4-dimethyl-4'-methoxybenzophenone or 2,4-dimethyl-4'-methylmercaptobenzophenone) and a one to one complex between the ketone and a Grignard reagent (methylmagnesium bromide) and approximately first order kinetics for the [RMgX] unit.

The preparation and properties of unsolvated organomagnesium halides have been studied to some extent.[52-54] Although their chemical properties parallel those of the the organomagnesium halides prepared in more basic solvents (e.g., in reactions with carbonyl compounds), no strict analogy can be drawn (e.g., unsolvated Grignards react with titanium (III) or (IV) chloride to form polymerization catalysts, a reaction which does not occur with solvated Grignards). Polymeric-like structures are indicated for these unsolvated organomagnesium halides, but not much work has been done yet to establish this.

Conclusion: It is evident from the studies made thus far that the question of the structure of the Grignard reagent has not yet been answered. Some recent comments support this view,[18,46] and it would seem that the major question now is why are the results thus far obtained of such variation. It could well be that the Grignard system inately consists of a number of possible equilibria and that the determination of which of these equilibria is to be favored is dependent on concentration, organic group, halogen, solvent and/or perhaps impurities. At any rate, definite conclusions do not exist at present.

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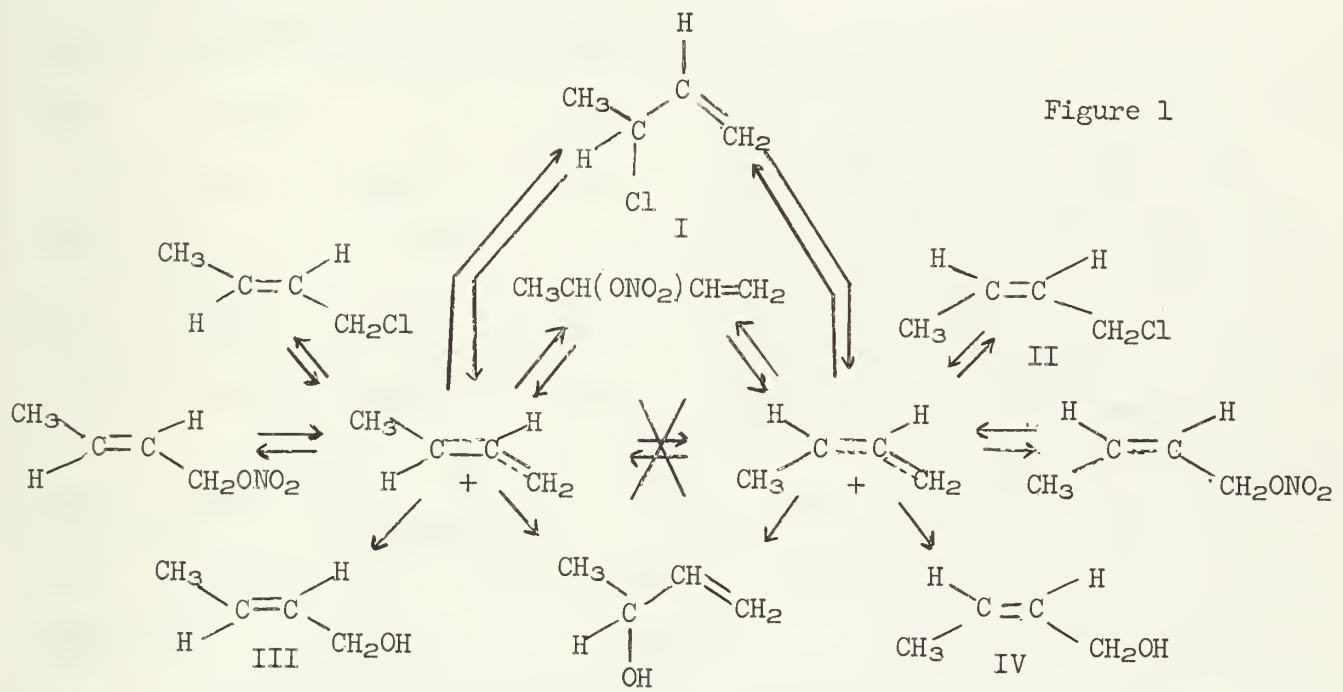
THE GEOMETRICAL STABILITY OF ALLYLIC CATIONS, ANIONS AND RADICALS

Reported by Nina Sussmann May 20, 1965

INTRODUCTION. - In resonance-stabilized allylic cations, anions and radicals there exists the possibility of cis-trans isomerization. It has been predicted that, since the C_β-C_γ bond still has partial double-bond character, a considerable barrier should exist to cis-trans isomerization and that geometry should be preserved.[1,2,3,4,5] On the other hand, it has been argued that resonance, which lowers the double bond character of the initial double bond, should make the system less rigid and thus permit geometrical isomerization.[6,7,8] This seminar will consider the problem of whether appropriately substituted open-chain allylic cations, anions and radicals can exist as discrete noninterconverting geometric isomers (cis and trans) which are chemically distinguishable or whether they rapidly equilibrate between the cis and trans configurations.

ALLYLIC CATIONS. - Silver Ion-Assisted Hydrolysis of Allyl Chlorides. -- In 1944 a brief investigation of the silver ion-promoted hydrolysis of crotyl and α-methylallyl chlorides gave some indication of cis-trans isomerization within the allylic cationic intermediate produced, but sufficiently accurate methods were not available to settle the question.[9] After the advent of vapor phase chromatography, the hydrolysis of the butenyl chlorides was further investigated by Young, Sharman and Winstein[1] using 0.090 N aqueous silver nitrate. The isomerization which they observed, as well as the formation of mixed butenyl nitrates, was explained by the following scheme:

Figure 1

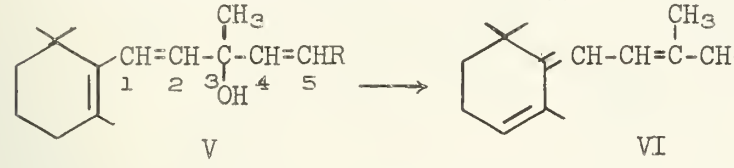


The crotyl alcohol from hydrolysis of cis-crotyl chloride (II) was nearly pure cis (IV) at the beginning of the reaction, but the proportion of trans isomer (III) increased steadily up to ca. 15%. The trans-crotyl alcohol was considered to arise from hydrolysis of α-methylallyl chloride (I) formed by concomitant intramolecular rearrangement of the starting material.[1,3] A plot of the percentage of crotyl alcohol which was trans against time indicated that the percentage of III approached 1% (±1%) at zero time. Thus, assuming that the hydrolysis of cis-crotyl chloride occurs solely by an S_N1 type process, retention of configuration in the cationic intermediate was of the order of at least 98%. However, the retention of configuration may result from the fact that in this example the allylic carbonium ion is very short-lived.[10] The possibility still exists that more stable longer-lived allylic cations in other systems might coordinate with a solvent molecule or another nucleophile more slowly than they lose configuration by rotation about the partial double bond.[1]

The "demercuration" of trans-crotylmercuric acetate by treatment with perchloric

acid in acetic acid has been found to be first order and to give a 71:29 mixture of α-methylallyl and crotyl acetates, respectively, in accord with a carbonium ion description for the solvolysis.[11] The crotyl component of the acetate product is nearly pure trans, in line with perservation of configuration by the trans-crotyl cation.

Rearrangement and Dehydration of a Substituted β-Ionol. -- Oroshnik and co-workers[12,13] have shown that 4,5-cis-V (R = $-CH_2C(CH_3)=CHCH_2OCH_3$) readily undergoes acid-catalyzed rearrangement and dehydration to give predominantly 4,5-cis- and 4,5-trans-VI. The appearance of 4,5-trans-VI cannot be due to a stereoisomerizing effect of the dehydrating agent on preformed 4,5-cis-VI, since it has been shown that the cis-trans ratio of the product is constant throughout the reaction.[13] The formation of both cis- and trans-isomers has been explained on the basis of a carbonium ion intermediate, since it is argued that only by the formation of an allylic carbonium ion center at C_3 can the 4,5-double bond become partly single and thus free to rotate, and has been cited as evidence for easy cis-trans interconversion in allylic carbonium ions.[6,7,13] However, the loss of configuration at the 4,5-linkage could also be due to formation of a neutral intermediate with a 4,5-single bond, e.g., an isomeric alcohol.[1] More must be known about the transformation in question before one can conclude that loss of configuration occurs in the allylic cation.



Hydrogenolysis with Chloroaluminum Hydride. -- In 1964 Brewster and Bayer[14] found that reduction of both cis- and trans-2,3-diphenyl-2-propen-1-ol (VII) with an aluminum chloride-lithium aluminum hydride mixture at or near room temperature gave predominantly cis-α-methyl stilbene (VIII). A third olefin, α-benzylstyrene (IX) was formed in amounts ranging from 20-40% of the hydrocarbon product. Reduction of trans-VII in ether at 80° (sealed tube) gave 39% trans- and 22% cis-VIII, while cis-VII gave 2.4% trans- and 69% cis-VIII. The results indicate that, although the last-mentioned reductions occur predominantly with retention of configuration, a pathway exists for interconversion of the geometrical isomers. This pathway cannot involve equilibration of the olefins, since it favors formation of the less stable α-methylstilbene and allows formation of quite large amounts of α-benzylstyrene, which should be the least stable of the three products. A control experiment showed that the olefins were not isomerized under the reaction conditions.

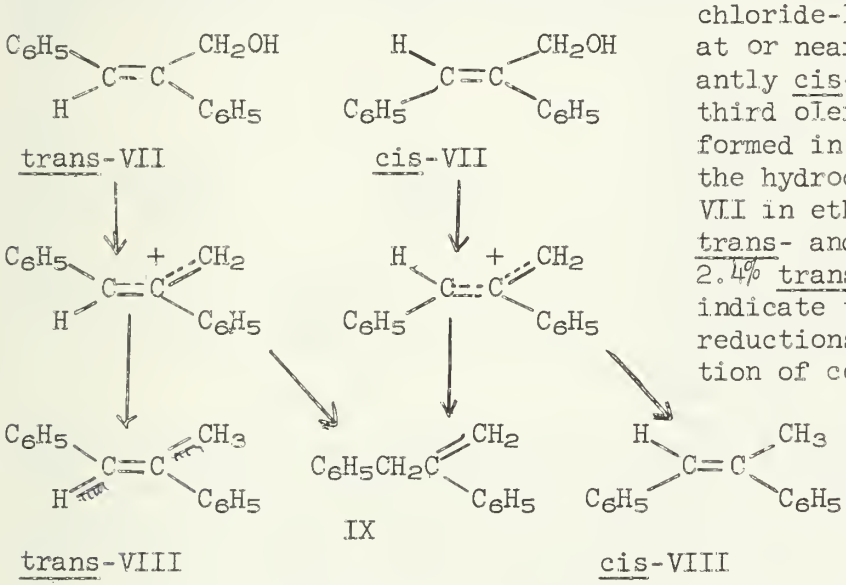


Figure 2

The relative reactivity of variously substituted benzylic alcohols[15,16] and of saturated alcohols,[17] together with the distribution of products from allylic alcohols,[14,18] indicate that the slow step of the hydrogenolysis involves the formation of a carbonium ion. It is suggested that ionization of the alcohol is preceded by formation of a chloroaluminum alkoxide, which then coordinates with a second molecule of Lewis acid, for example, as in Figure 3. Brewster and Bayer suggest that isomerization of the trans carbonium ion to the cis occurs by a reversal of the ionization to form a derivative of α-styrylphenylcarbinol (X).[14] Such a process is consistent with the observation that an increase in the concentration of hydride donor produces a decrease in the fraction of cis olefin in the product from reduction of trans alcohol, since attack of hydride donor would compete with equilibration of the isomeric allylic carbonium ions. Furthermore, it is found that X is reduced more rapidly than

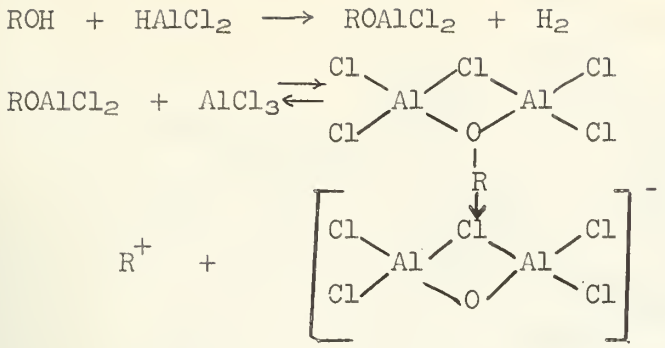
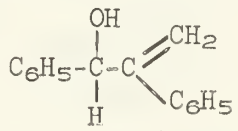


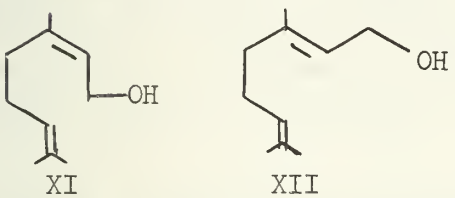
Figure 3

cis- and trans-VII to give a distribution of olefins intermediate between that from cis- and trans-VII. However, these results are also consistent with the possibility not considered by Brewster that the trans allylic carbonium ion can isomerize to the cis allylic carbonium ion by rotation about the C_2C_3 bond without passing through an α-styrylphenylcarbinyl derivative.



X

Hydrogenolysis of nerol (XI) and geraniol (XII) suggested that the geometric configuration of the original double bond was retained to a high degree in the allylic carbonium ions produced.[18] About 87% of the product from XI, but only 8% of that from XII, was cyclic. However, the greater cyclization of XI could result from a different mechanism involving synchronous double bond attack and ionization.



XI XII

ALLYLIC ANIONS. - Sodium-on-Alumina-Catalyzed Isomerization of n-Butenes. -- In 1960 Haag and Pines[19] reported that the sodium-on-alumina-catalyzed isomerization of 1-butene and of cis-2-butene at 30° gave the same equilibrium mixture of 1-butene (3%), trans-2-butene (75%) and cis-2-butene (22%). The data indicated that the isomerization is a reversible parallel reaction of the type shown in Figure 4. Starting with each of the three isomers, the following ratios were obtained from the concentrations of the other two isomers formed: $k_3/k_1 = 4.0$, $k_4/k_6 = 1.3$, $k_5/k_2 = 3.6$. The double bond shift and the cis-trans isomerization are considered to occur by a chain mechanism involving allylic carbanion intermediates.[19,20] Infrared spectra of allylic alkenylsodium compounds give some evidence for the existence of two distinct isomers, cis and trans.[2,21] According to the rate data for isomerization of the butenes, protonation of the cis-carbanion to give cis-2-butene occurs four times more frequently than protonation of the trans-carbanion to give trans-2-butene. This preferred protonation at the terminal carbon of the cis anion might result from greater reactivity of the cis-butenyl anion, in which case the cis- and trans-butenyl carbanions must interconvert faster than the protonation reaction, or, alternatively, from a higher concentration of the cis-carbanion than of the trans-carbanion.[19] Haag prefers the latter interpretation, suggesting that higher concentration of cis-butenylsodium might result from stabilization by an additional resonance structure (XIII).[19,20]

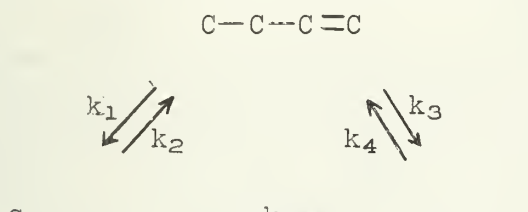
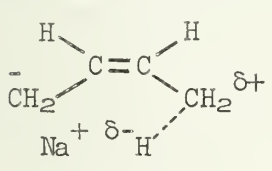


Figure 4



XIII

t-Butoxide-Catalyzed Isomerization of cis- and trans-α-Methylstilbene -- In 1962 Zwierzak and Pines[22] reported that cis- and trans-α-methyl stilbene (XV) were equilibrated in the presence of catalytic amounts of potassium t-butoxide at 139° in xylene to give an equilibrium mixture consisting of 21.0% cis-XV, 76.8% trans-XV and 2.2% 2,3-diphenyl-1-propene (XIV). The cis-trans isomerization, which was much slower than the double bond migration to give XIV, was believed to result from rotation around the partially single C_2C_3 bond of the allylic carbanion formed as intermediate.

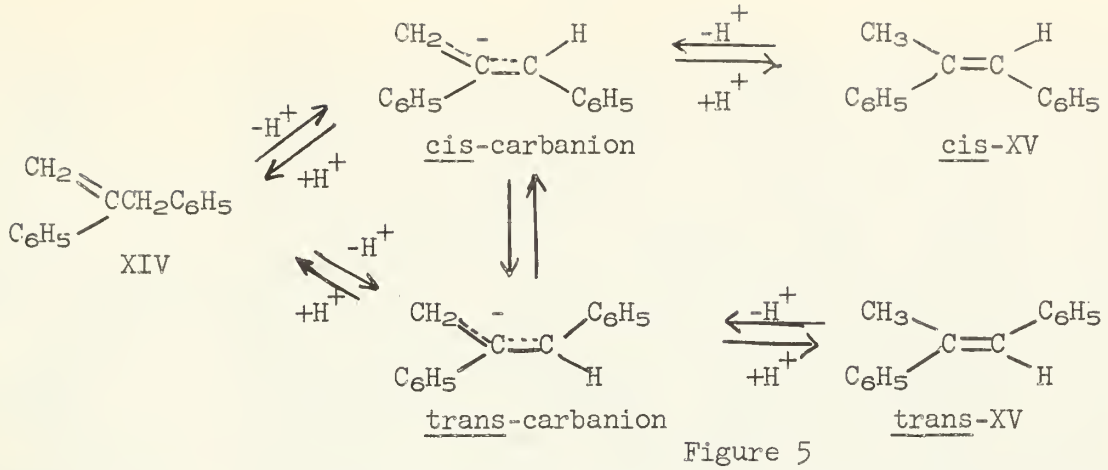


Figure 5

In 1964 the t-butoxide catalyzed isomerization and hydrogen-isotope exchange reactions of cis- and trans-XV and XIV were studied by Cram and Hunter[23] in t-butyl alcohol and t-butyl alcohol-O-d. Two general mechanisms were considered, which may be regarded as limiting cases of the more general mechanism shown in Figure 5. In one of these mechanisms, noninterconverting cis- and trans-allylic anions were

cis-XV ⇌ cis-carbanion ⇌ XIV ⇌ trans-carbanion ⇌ trans-XV

Model A

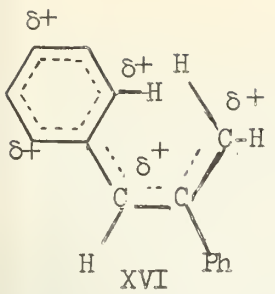
treated as intermediates (Model A), and in the other rapidly equilibrating cis and trans anions or a single anion were regarded as intermediates (Model B). The consistency between the data and the two mechanisms was examined using two approaches. In the first, the kinetic data of isomerization and deuterium incorporation were applied to each model and equilibrium constants between cis-XV and XIV were calculated. The value of the equilibrium constant, $(\text{cis-XV/XIV})_e$, for equilibrium between cis-α-methylstilbene and α-benzylstyrene was calculated from model A to be 10.3 ± 1.5 and from model B to be 102 ± 15. Comparison of these calculated values with the experimentally determined value, $(\text{cis-XV/XIV})_e = 10.1 \pm 0.5$, shows good agreement between the value found and that calculated based on model A, but a decided lack of agreement between the observed value and that calculated on model B. In the second approach, model A was subjected to a detailed kinetic analysis through use of an IBM 7090 computer. Predictions based on model A were found to be in good agreement with experiment. Thus, it appears that the cis- and trans-allylic anions collapse to their respective olefins without undergoing appreciable interconversion. Interconversion of cis- and trans-XV occurs mainly through XIV.

cis-XV ⇌ carbanion ⇌ trans-XV
↓↑
XIV

Model B

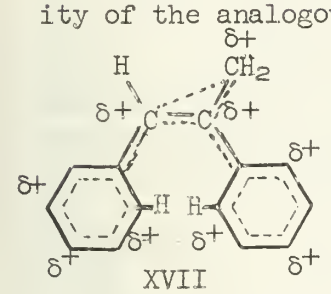
Kinetic data indicated that the collapse of cis-carbanion favors cis-XV over XIV by a factor of 6.5, whereas the collapse of trans-carbanion favors trans-XV over XIV by a factor of 8.8. In the isomerization of XIV the ratio trans-XV/cis-XV = 11 is maintained over much of the reaction. These values indicate that the transition state for the production of trans-carbanion is more stable than that for production of cis-carbanion and suggest that the trans-allylic anion is more stable than the cis-allylic anion.[23] This conclusion is considered by Cram to be in accord with what might be expected on structural grounds. He believes that in the cis-carbanion coplanarity of the directly conjugated benzene ring and the allylic π-system is sterically inhibited more than in the trans-carbanion. Hence, greater delocalization of negative charge should make the trans-carbanion more stable. Since t-butyl alcohol is a nondissociating medium, the carbanions are probably part of an ion-pair. Cram argues that delocalization of negative charge in the trans-carbanide ion-pair would not involve as much charge separation as in the more elongated cis-carbanion and that this effect might also contribute to the greater stability of the trans-carbanion.

The greater stability of the trans-carbanion contrasts with the results obtained with the analogous carbonium ions generated from cis- and trans-2,3-diphenyl-2-propen-1-ol and reduced to α-methyl stilbene with chloroaluminum hydride.[17] As has been noted in



XVI

an earlier section, the cis-carbonium ion largely retained its geometrical integrity, but the trans-carbonium ion retained only part of its integrity. From these results Brewster[17] concluded that in his system the cis-carbonium ion is more stable than the trans-ion. He ascribed the lesser stability of the trans-carbonium ion to coulombic repulsion or perhaps to steric hindrance of coplanarity (XVI). However, these arguments are similar to those of Cram[23] for the greater stability of the analogous trans-carbanion. It seems likely that phenyl-phenyl interaction in the cis-carbonium ion would be greater than that of methylene-phenyl interaction in the trans-carbonium ion, as predicted by Cram for the carbanions, especially in view of recent n.m.r. evidence[24] for the strong contribution of 1,3-π-interactions in allylic cations. According to valence bond treatment of the allylic cation, 1,3-π-interactions should place excess positive charge on the central carbon atom, as well as on the terminal positions.[25] The phenyl group at C-2 of trans-2,3-diphenyl-2-propen-1-ol would be expected to delocalize positive charge at the C-2 carbon of the trans-carbonium ion, but in the cis-carbonium ion steric hindrance to coplanarity of the two phenyls might be expected (XVII).



XVII

Cram[23] finds the difference in behavior of the two kinds of charged species difficult to understand, but suggests that it might be associated with differences in their lifetimes. In the carbanion study, proton capture was probably extremely rapid and the carbanion lifetime very short, while in the carbonium ion study, the hydride capture was probably much slower and the carbonium ion lifetime greater. It is evident that protonation of the anions is faster than their equilibration, and thus the predominant stereochemistry of the olefins appears to be determined not by the relative reactivities of the cis and trans anions, but rather by their relative concentrations, i.e., by their relative stabilities. However, in the carbonium ion study, the fact that more cis than trans olefin is formed in the reduction of both cis and trans-2,3-diphenyl-2-propen-1-ol does not necessarily require that the cis allylic carbonium ion be more stable than the trans. It is possible that the cis carbonium ion undergoes hydride capture faster than the trans carbonium ion and that its faster consumption pulls the equilibrium toward the cis carbonium ion, even though the trans ion may be more stable. Greater formation of the cis olefin than of the trans olefin is also favored by the fact that, while the trans-carbonium ion is reduced almost to the same extent at either end, the cis ion is reduced chiefly (82%) to cis-α-methyl stilbene.[14]

Assuming, as suggested by Brewster,[14] that the cis-carbonium ion is more stable than the trans-carbonium ion produced in the hydrogenolysis of the 2,3-diphenyl-2-propen-1-ols, its greater stability might be explained by considering the reaction as an ionization to an ion pair, as would probably be expected in the ethereal solvent used. Steric factors resulting from association of the carbonium ion with the bulky, bridged, aluminum-containing anion shown in Figure 3 might be expected to favor the cis configuration of the carbonium ion.

ALLYLIC RADICALS. - Chlorination of Olefins with t-Butyl Hypochlorite. -- In 1961 Walling and Thaler[26] reported that complete retention of cis-trans geometry was observed in the allylic chlorination of the 2-butenes with t-butyl hypochlorite at 0° and at 40°; trans-2-butene gave trans-1-chloro-2-butene, while cis-2-butene gave 1-chloro-2-butene which was completely cis (Figure 6.) Similar results were obtained

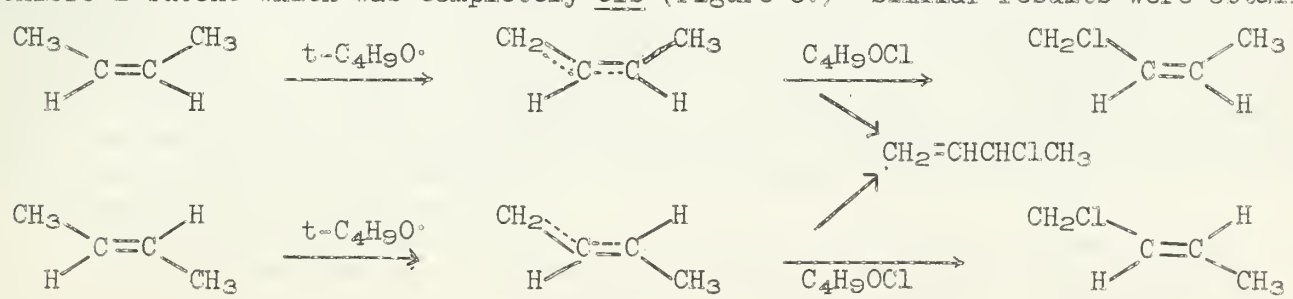


Figure 6

with the 2-pentenes at 40° and below and with the 4,4-dimethyl-2-pentenes at -78°. Such results are incompatible with the assumption of a common intermediate radical arising from the isomeric cis and trans olefins, and indicate that cis- and trans-allylic radicals are capable of retaining their stereochemistry until they react with t-butyl hypochlorite to yield the observed products.[26] However, with increasingly bulky groups, the cis-allylic radicals are sufficiently destabilized so that rotation can occur at higher temperatures. Thus, cis-2-pentene gave some trans product at 100°, while cis-4,4-dimethyl-2-pentene gave a stereochemically clean reaction only at -78°. Although a small amount of addition of t-butyl hypochlorite to give β-chloroalkyl t-butyl ethers accompanied substitution, there was no evidence that reversibility of the addition accounted for the failure of the allylic substitution to remain completely stereospecific at high temperatures, since no cis-trans isomerization of unreacted olefins could be detected.

Walling and Thaler[26] also studied the stereochemical consequences of double bond shifts during chlorination of 1-olefins. If it is granted that allylic radicals can retain their stereochemistry during the reaction, the stereochemistry of the 1-chloro-2-olefins produced must reflect the composition of the allylic radicals formed at the instant of attack on the olefin by the t-butoxy radical. This, in turn, ought to be determined by the conformational distribution of the olefin at the moment of reaction. Assuming a staggered conformation about C_2C_3 of the double bond and the groups on C_3, trans- and gauche conformations are possible, which should give rise to trans and cis products, respectively (Figure 7). Although the gauche structure is statistically favored, it becomes increasingly sterically hindered as the size of R increases, and the trans structure should become more stable. The results are consistent with this picture. For R = methyl, R = ethyl, and R = t-butyl the products are, respectively, 63%, 75%, and 100% trans. Alternatively it is possible that potential minima exist for olefin conformations about C_2C_3 where CH_2 = is eclipsed (Figure 8),[27] in which case it also seems evident that the cis-allylic radical would suffer from increasing intergroup repulsion with increasing size of R.[26]

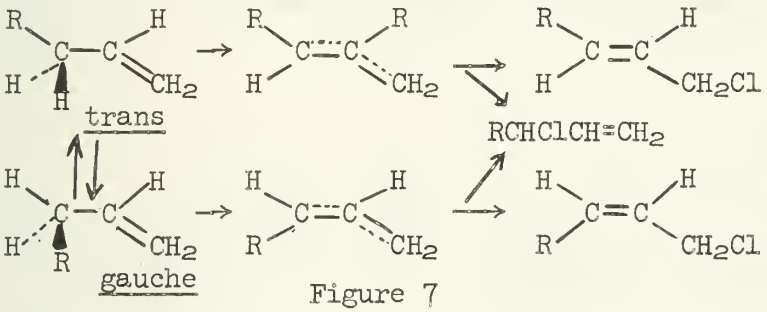


Figure 7

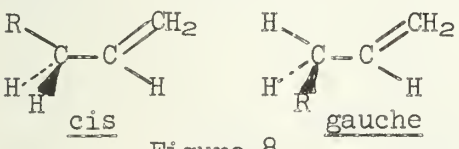


Figure 8

Reaction of Thiols with Conjugated Dienes. -- Thaler, Oswald, and Hudson[28] have recently studied the stereochemistry of the addition and cooxidation reactions of thiols with cis- and trans-1,3-pentadiene (XVIII). The free radical addition of thiols to 1,3-pentadiene yields mainly the 1,2 and 1,4 adducts resulting from attack of the thiyl radical at C_1 of pentadiene. The reaction of thiols with dienes in the presence of oxygen (cooxidation) also involves the addition of thiyl radical at C_1 of the diene to give an allylic radical. Removal of a hydrogen atom from the thiol then gives hydroperoxide, which in the presence of catalytic quantities of amine is immediately reduced by excess thiol to allylic alcohol.

The addition and cooxidation of benzenethiol with cis- and trans-XVIII were highly specific, with the 1,2 adducts and adduct alcohols retaining essentially the same geometry as the dienes from which they were derived. Thus, it appears that different allylic radicals, which maintain their steric configuration, are involved in these reactions of cis- and trans-XVIII.[28] Although the cooxidation of benzenethiol proceeds without any isomerization of reacting diene, the addition of benzenethiol causes significant cis-trans isomerization of XVIII. Most of the isomerization occurs at the latter portion of the reaction, however, and has little effect on the stereospecificity of the product.

Although the addition of aliphatic thiols occurred without isomerization of the reacting 1,3-pentadiene, the products showed little retention of configuration. However, the observation of some preference for cis-1,2-adduct from cis-XVIII and

trans-1,2-adduct from trans-XVIII suggests that while the intermediate radicals undergo considerable isomerization under these conditions, they are still not interconverting freely.[28]

The differences in stereochemistry of the 1,2 products observed between aromatic and aliphatic thiols, and between addition and cooxidation reactions, can be rationalized by the scheme in Figure 9, which depicts potential reaction paths for the more stable transoid conformations of cis- and trans-XVIII.

The interconversion of the intermediate allylic radicals should be a function of their lifetime. Slower consumption of the radicals should provide greater opportunity for rotation and consequent destruction of stereospecificity. The S-H bond of aromatic thiols is weaker than that of aliphatic thiols, since the thiyl radical resulting from scission of the former bond can be stabilized by resonance with the phenyl ring. As a result, the abstraction of a hydrogen from methanethiol (R = CH_3) should be more difficult than from benzenethiol (R = Ph). Since $k_3(PhSH) > k_3(CH_3SH)$, more isomerization of the intermediate allylic radical should be possible with methanethiol.[28]

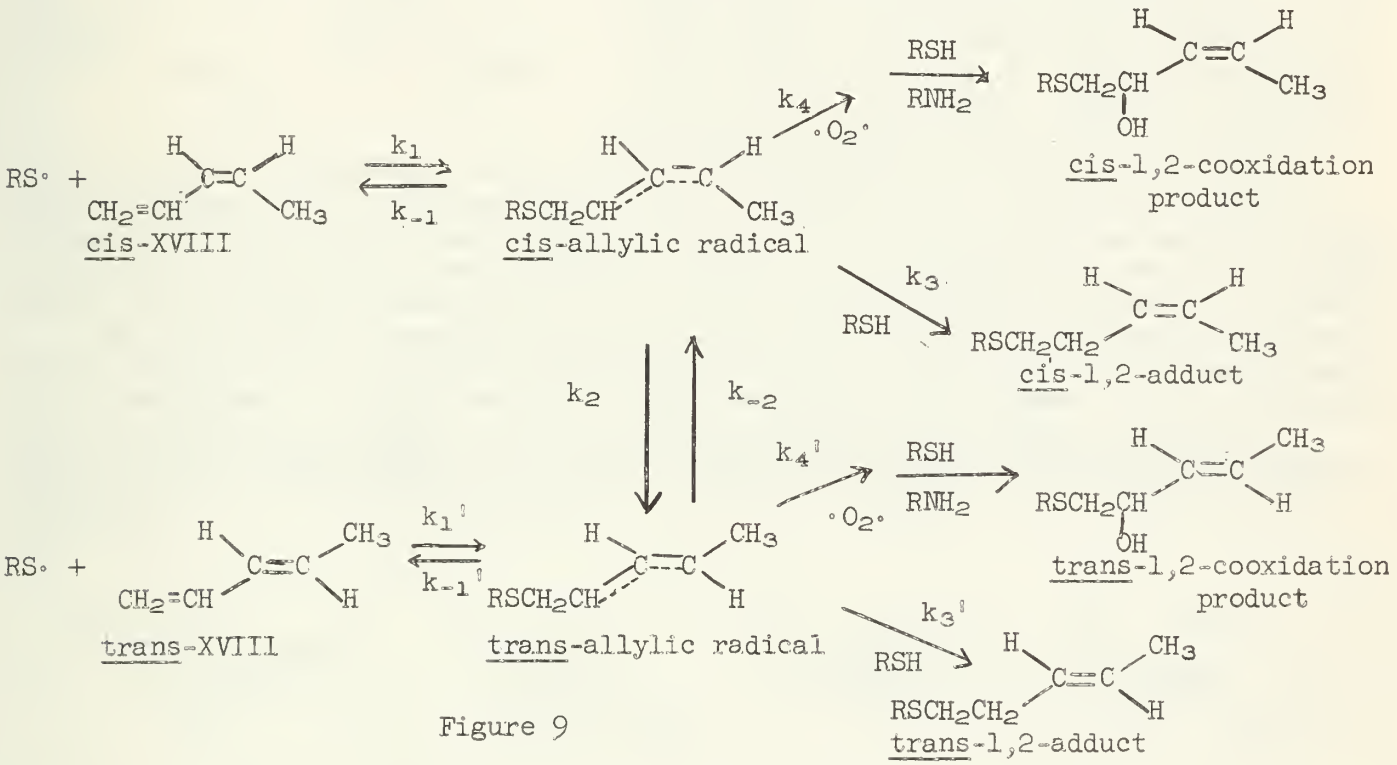


Figure 9

The observation that benzenethiol addition leads to isomerization of unreacted 1,3-pentadiene, while methanethiol addition does not, suggests that benzenethiol addition is reversible while methanethiol addition is not. As a consequence of the difference in stability of aromatic and aliphatic thiyl radicals, the addition of PhS· to XVIII would be expected to be more reversible than the addition of CH_3S· [$k_{-1}(R = Ph) > k_{-1}(R = CH_3)$].[28]

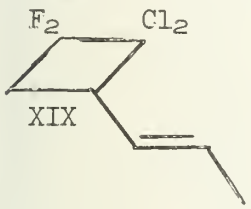
The observation that the preferential coupling of the intermediate allylic radical with oxygen, a process which presumably requires lower activation energy ($k_4 \gg k_3$) than abstraction of hydrogen from thiol, eliminates any isomerization of diene and gives 1,2 adducts with complete retention of configuration is also consistent with the scheme. Apparently, the reaction of the intermediate allylic radical with oxygen is a very rapid step ($k_4 > k_{-1} \gg k_3$).

The 1,4 adduct from the addition of benzenethiol to cis-XVIII was 92% trans, and the 1,4 adduct from trans-XVIII was essentially pure trans (99+%). If the intermediate radicals maintain their configuration about the C_2C_3 bond no less than about the C_3C_4 bond, then the geometry of the 1,4 addition product should be the same as that of the rotational conformation of XVIII which is attacked by thiyl radical. Since investigation of the conformational distribution of dienes such as butadiene[29] has shown that the transoid conformation predominates over the cisoid conformation,

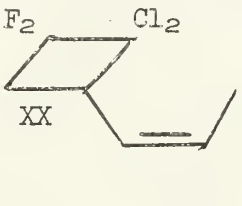
the observed formation of mainly trans-1,4 adduct is expected from retention of configuration by the intermediate allylic radical.[28]

Butadiene Polymerization. -- In the free radical polymerization of butadiene more cis double bonds are produced in the polymer than would be expected from existence of butadiene predominantly in the transoid conformation.[28,30] Lack of direct correlation between the structure of the product and the conformational distribution of the diene can perhaps be attributed to isomerization of the intermediate allylic radicals which are produced.[28] The fact that higher temperatures, which would increase the rate of isomerization of allylic radicals as well as increase the relative stability of the cis radical, give increasing amounts of cis polymer is consistent with this interpretation.

Cycloaddition of 1,1-Dichloro-2,2-Difluoroethylene. -- In 1964 Bartlett, Montgomery and Seidel[31] reported that 1,1-dichloro-2,2-difluoroethylene reacts stereospecifically with trans-1,3-pentadiene to give 1,1-difluoro-2,2-dichloro-3-trans-propenylcyclobutane (XIX) and with cis-1,3-pentadiene to give 1,1-difluoro-2,2-dichloro-3-cis-propenylcyclobutane (XX) by a two-step mechanism involving a biradical intermediate. During the addition to cis- and trans-1,3-pentadiene the double bond in whose configuration the two starting materials differ becomes part of an allylic radical in the intermediate. Thus, the retention of configuration during the addition demonstrates that the allylic diradical intermediates can maintain their configuration during the time interval required for the coupling of unpaired electrons and provides another illustration of the stereochemical stability of allylic radicals.



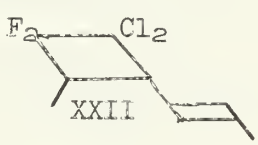
XIX



XX

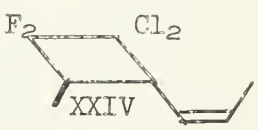
The absence of stereoequilibration in the side-chain double bond was confirmed by the addition of 1,1-dichloro-2,2-difluoroethylene to the three geometrical isomers of 2,4-hexadiene.[32] Under conditions where the geometrical isomers of 2,4-hexadiene, as well as their 1,2 adducts with 1,1-dichloro-2,2-difluoroethylene, undergo no isomerization, trans,trans-2,4-hexadiene yielded XXI and XXII, cis,cis-2,4-hexadiene yielded XXIII and XXIV and trans,cis-2,4-hexadiene yielded all four cycloaddition products.

XXI



XXII

XXIII



XXIV

These are the products which would be expected if the reaction proceeds through a bifunctional intermediate in which ring closure competes with rotation about the bond which was originally double and in which the nonparticipating double bond retains its configuration.

Roberts and Sharts[33] have suggested that the reaction of tetrafluoroethylene with butadiene to give exclusively the 4-membered ring adduct, while cyclopentadiene yields both 1,2 and 1,4 addition products, can be explained in terms of the stereochemical stability of allylic radicals. With cyclopentadiene the double bonds can have only the quasi-cis relationship to one another, and the diradical would necessarily possess the configuration which would afford both 4 and 6 membered ring products. On the other hand, any diene which is not constrained to the cisoid conformation probably exists predominantly in the transoid conformation, and in the bifunctional intermediate the 4-position is too remote in space from the $-CF_2-$ function to be a likely point of ring closure. A 6-membered ring could only be formed if the allyl-type radical were able to lose momentarily its resonance stabilization through a twist about the C_2C_3 bond or the C_3C_4 bond.

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